Glucose Intolerance as a Predictor of Hypertension in Pregnancy

Caren G. Solomon, Steven W. Graves, Michael F. Greene, Ellen W. Seely

Abstract  Insulin resistance is associated with and may be causal in essential hypertension, but the relation between insulin resistance and hypertension arising de novo in pregnancy is unclear. Transient hypertension of pregnancy (new-onset nonproteinuric hypertension of late pregnancy) is associated with a high risk of later essential hypertension and thus may have similar pathophysiology. To assess the association between glucose intolerance and subsequent development of proteinuric and nonproteinuric hypertension in pregnancy in women without underlying essential hypertension or overt glucose intolerance, we performed a retrospective case-control study comparing glucose levels on routine screening for gestational diabetes mellitus among women subsequently developing hypertension. Women who developed hypertension in pregnancy (n=97) had significantly higher glucose levels on 50-g oral glucose loading test (P<.01) and a significantly higher frequency of abnormal glucose loading tests (≥7.8 mmol/L) (P<.01) than women who remained normotensive (n=77). Relative glucose intolerance was particularly common in women who developed nonproteinuric hypertension.

E  sential hypertension is associated with glucose intolerance and insulin resistance. The observation of increased insulin resistance in normotensive offspring of hypertensive parents suggests that insulin resistance precedes the development of essential hypertension and may be causal. Postulated mechanisms by which insulin resistance or hyperinsulinemia may predispose to hypertension include increased renal sodium reabsorption, activation of sympathetic nervous system activity, and stimulation of cell membrane cation transport.

The role of insulin resistance in the pathogenesis of hypertension arising de novo in pregnancy has received little attention, but indirect evidence suggests it may be important. Pregnancy is a state of increased insulin resistance; hypertension in pregnancy characteristically presents in the third trimester when the insulin resistance normally accompanying pregnancy is greatest. Obesity, which is associated with a decreased sensitivity to insulin, may be a risk factor for hypertension in pregnancy. In addition, an increased risk of hypertension in pregnancy has been reported in some studies of gestational diabetic women. A role for insulin resistance in at least some cases of new-onset hypertension in pregnancy is also suggested by the association of transient hypertension, or new-onset nonproteinuric hypertension of late pregnancy, with a high incidence of later essential hypertension.

To assess whether glucose intolerance and insulin resistance are associated with an increased risk of hypertension in pregnancy among women without essential hypertension or overt glucose intolerance, we performed a case-control study comparing glucose levels at the time of routine screening for gestational diabetes mellitus among nondiabetic women subsequently developing hypertension and women remaining normotensive to term. The group with hypertension developing in late pregnancy was subdivided into those women with preeclampsia (new-onset proteinuric hypertension) and those with transient hypertension (new-onset nonproteinuric hypertension).

Methods

Subjects

The study population consisted of 97 women with new-onset hypertension in pregnancy and 77 normotensive women giving birth at Brigham and Women’s Hospital and identified by hospital diagnosis. New-onset hypertension in pregnancy was defined as a systolic blood pressure (SBP) of 140 mm Hg or greater or diastolic blood pressure (DBP) of 90 mm Hg or greater, constituting a rise in SBP of 30 mm Hg or greater or in DBP of 15 mm Hg or greater over first-trimester values measured on at least two occasions more than 6 hours apart and developing after 24 weeks of gestation in a previously...
Demographic and Clinical Variables in Women Developing New-Onset Hypertension in Pregnancy, Either Preeclampsia or Transient Hypertension, and Women Remaining Normotensive to Term

<table>
<thead>
<tr>
<th></th>
<th>Hypertension in Pregnancy</th>
<th>Preeclampsia</th>
<th>Transient Hypertension</th>
<th>Normotensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=97)</td>
<td>(n=50)</td>
<td>(n=47)</td>
<td>(n=77)</td>
</tr>
<tr>
<td>Age, y</td>
<td>30.9 (5.0)</td>
<td>31.2 (4.8)</td>
<td>30.6 (5.3)</td>
<td>29.5 (4.3)</td>
</tr>
<tr>
<td>Race, % white/Hispanic/black</td>
<td>76/8/15</td>
<td>70/10/20</td>
<td>83/6/11</td>
<td>80/8/12</td>
</tr>
<tr>
<td>First pregnancy, %</td>
<td>36</td>
<td>42</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>Gestational age at GLT, wk</td>
<td>28.4 (1.7)</td>
<td>28.3 (2.0)</td>
<td>28.5 (1.3)</td>
<td>28.2 (1.5)</td>
</tr>
<tr>
<td>Pregravid BMI, kg/m²</td>
<td>24.6 (4.4)</td>
<td>24.4 (3.7)</td>
<td>24.8 (5.1)</td>
<td>22.0 (3.4)$#$</td>
</tr>
<tr>
<td>Weight gain, kg</td>
<td>12.2 (5.2)</td>
<td>13.3 (5.8)</td>
<td>11.0 (4.2)</td>
<td>10.1 (4.1)$#$</td>
</tr>
<tr>
<td>BP at baseline, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>115 (9)</td>
<td>115 (9)</td>
<td>115 (9)</td>
<td>107 (9)$#$</td>
</tr>
<tr>
<td>Diastolic</td>
<td>71 (7)</td>
<td>71 (7)</td>
<td>71 (6)</td>
<td>65 (6)$#$</td>
</tr>
<tr>
<td>BP at GLT, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>120 (11)</td>
<td>121 (12)</td>
<td>119 (10)</td>
<td>110 (8)$#$</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73 (8)</td>
<td>73 (10)</td>
<td>73 (6)</td>
<td>66 (5)$#$</td>
</tr>
</tbody>
</table>

GLT indicates glucose loading test; BMI, body mass index; and BP, blood pressure. Values are mean (SD).

*a*Weight gain calculated from reported prepregnancy weight to GLT weight.

$^tP<.0001$, $^P<.01$, hypertension in pregnancy vs normotensive.

$^\#P<.0001$, $^P<.01$, preeclampsia vs normotensive.

$^tP<.001$, $^P<.0001$, transient hypertension vs normotensive.

nor normotensive woman. Forty-seven of the hypertensive women had transient hypertension, defined as hypertension without significant proteinuria (24-hour urinary protein <300 mg). The other 50 women had preeclampsia, defined as hypertension in association with 24-hour urinary protein of 300 mg or greater or, in the absence of a 24-hour urinary protein measurement, proteinuria of at least 2+ on dipstick.

The normotensive control group included women who did not develop hypertension during pregnancy or in the immediate postpartum period. Control subjects were initially selected by matching to hypertensive subjects for age, race, and gestational age at the time of glucose loading test (GLT), used to screen for gestational diabetes mellitus. However, because matching proved inefficient and any imbalance between groups could be adjusted for in multivariate analyses, in the later stages of the study control subjects were selected without regard to matching criteria.

To avoid inclusion of essential hypertensive women in the transient hypertensive or preeclamptic groups, we excluded women who were unable to document a normal blood pressure reading in the first trimester, or, if this was unavailable, in the 6 months preceding pregnancy or at a 6-week postpartum visit. Women were also excluded if they had any underlying medical illness, such as renal or liver disease, connective tissue disease, diabetes antedating pregnancy, or gestational diabetes mellitus or were taking any medications that could have affected glucose tolerance. Women not having a GLT between 24 and 32 weeks of gestation were likewise excluded. GLTs were performed at random times of day irrespective of meals and consisted of a 50-g oral glucose load followed by plasma glucose measurement 60 minutes later; a plasma glucose level of 7.8 mmol/L or greater on this test is considered abnormal and an indication for a 3-hour oral glucose tolerance test to exclude gestational diabetes mellitus.11

The study was approved by the Human Research Committee of Brigham and Women’s Hospital.

Data Collection

We reviewed medical records to obtain the following demographic and clinical data on all study subjects: age; race; gravidity and parity; height; reported prepregnancy weight, first-trimester weight, and weight at time of GLT; gestational age at GLT; and blood pressures in the first trimester and at GLT. Documentation of first-trimester blood pressure was unavailable for six women in whom normal blood pressure measurement in the 6 months preceding pregnancy or at a 6-week postpartum office visit was used as the “baseline” blood pressure measurement. Prepregnancy body mass index (BMI) and at the time of GLT was calculated by dividing weight in kilograms by height in meters squared. If a subject was not evaluated at her physician’s office the day of the GLT, her weight at the visit closest in time to this screening test was used to estimate BMI at the time of GLT.

Insulin levels were measured by radioimmunoassay on a subset of 80 women (33 with hypertension in pregnancy, 47 normotensive) who had their GLTs performed at Brigham and Women’s Hospital and had serum stored at −20°C at the time of GLT. The assay was made with a commercial kit (Diagnostic Products) according to the manufacturer’s protocol.

Statistical Analysis

Means and standard deviations are presented. Continuous data were compared between hypertensive and normotensive subjects using the Wilcoxon rank sum test. Women with transient hypertension and women with preeclampsia were each compared with the normotensive group using the Kruskal-Wallis test; post hoc pairwise comparisons between each hypertensive subgroup and the normotensive group were done using the Wilcoxon rank sum test. Discrete data were analyzed using the $\chi^2$ test. For all post hoc pairwise comparisons, a value of $P<.025$ was considered statistically significant. Logistic regression was used for multivariate analysis.

Results

Women who developed new-onset hypertension in pregnancy did not differ significantly from women who remained normotensive in mean age, gestational age at GLT, or race (Table 1). Women who developed hypertension and women who remained normotensive were equally likely to be primigravid; however, primigravidity was slightly more common among women who developed preeclampsia than among normotensive women.
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Although all groups had normal blood pressures at baseline as required by study entry criteria, women who developed hypertension had significantly higher baseline SBP (115 versus 107 mm Hg) and DBP (71 versus 65 mm Hg) than women remaining normotensive to term (P<.0001 for both). Both women who developed transient hypertension and women who developed preeclampsia differed significantly from women who remained normotensive in baseline blood pressures (P<.0001). At the time of GLT, women who developed hypertension also had significantly higher SBP (120 versus 110 mm Hg) and DBP (73 versus 66 mm Hg) than women who remained normotensive (P<.0001 for both) (Table 1).

Pregravid and first-trimester BMIs were also significantly greater in women who developed transient hypertension or preeclampsia than in women who remained normotensive (P<.0001 for both). Weight gain from reported prepregnancy weight to weight at GLT was significantly greater in women developing hypertension than in normotensive women, a difference largely explained by the significantly higher weight gain in women who developed preeclampsia; weight gain among women who developed transient hypertension differed little from that among women remaining normotensive.

Glucose levels at the time of GLT were significantly higher in women who later developed hypertension than in women who remained normotensive (6.7 versus 6.0 mmol/L, P<.01). When hypertensive subgroups were evaluated separately, women who developed transient hypertension had significantly higher glucose levels (6.9 mmol/L) than normotensive control women, whereas glucose levels in women with preeclampsia were intermediate (6.5 mmol/L) and not significantly different from those of normotensive women by post hoc pairwise comparisons (Fig 1). Glucose levels did not differ significantly between primigravidas (6.6±1.3 mmol/L) and multigravidas (6.4±1.3 mmol/L) who developed preeclampsia.

Insulin levels measured at the time of GLT on a subset of women tended to be higher among women who developed hypertension in pregnancy (582±402 pmol/L, n=33) than among those who remained normotensive (438±258 pmol/L, n=47), although differences were not statistically significant. Insulin levels were similar among women developing transient hypertension (560±423 pmol/L, n=22) and women developing preeclampsia (610±423, n=11). Likewise, insulin-glucose ratios did not differ significantly between women who developed hypertension and those who remained normotensive (data not shown).

No absolute glucose level distinguished reliably between women developing new-onset hypertension in pregnancy and normotensive women. Still, a significantly higher percentage of women who developed hypertension (27%) than remained normotensive (9%) had GLT glucose levels of 7.8 mmol/L or greater (P<.01). When hypertensive subgroups were examined separately, 36% of women developing transient hypertension had GLT glucose levels of 7.8 mmol/L or greater (P<.0001 versus normotensive group), whereas 18% of women developing preeclampsia had glucose levels in this range (P=NS versus normotensive) (Fig 2).

Results of a multivariate analysis assessing risk for new-onset hypertension in pregnancy associated with a GLT glucose level of 7.8 mmol/L or greater are shown in Table 2. After adjustment for maternal age, race (white versus nonwhite), and gestational age at GLT, high glucose levels were associated with a significantly increased risk of hypertension (P<.01). These results were not simply explained by greater adiposity in the women who became hypertensive; after adjustment for prepregnancy BMI, GLT glucose levels of 7.8 mmol/L or greater remained an independent predictor of hypertension (P<.05). In separate analyses by subtypes of hypertension in pregnancy, a GLT glucose level of 7.8 mmol/L or greater remained an independent predictor of transient hypertension (P<.01) but not preeclampsia after adjustment for maternal age, race, gestational age at GLT, and pregravid BMI.

Discussion

Insulin resistance is associated with and may be causal in essential hypertension.1-5 The results of the present study indicate a strong association between glucose intolerance and subsequent development of hypertension in pregnancy, particularly in the nonproteinuric subtype. This finding is particularly notable in that women with essential hypertension or overt glucose intolerance were carefully excluded.
An association between insulin resistance and hypertension in pregnancy was initially suggested by reports of higher glucose levels on intravenous glucose tolerance testing,\textsuperscript{12} attenuated glucose response to intravenous insulin,\textsuperscript{13} and elevated insulin levels in response to a glucose load\textsuperscript{14} among women with preeclampsia. However, these studies included small numbers of patients, did not explicitly differentiate preeclampsia from transient hypertension, and did not systematically eliminate women with preexisting essential hypertension. More recently, a hyperinsulinemic response to oral glucose load was reported among non-preeclamptic hypertensive pregnant women compared with normotensive control women;\textsuperscript{15} these results are difficult to interpret in that essential hypertensive women were not excluded and many of the subjects used illicit drugs, which may have affected insulin dynamics. Because glucose tolerance was assessed in all of these studies after the onset of hypertension, changes in insulin sensitivity related to stress (glucocorticoids) or systemic complications of preeclampsia or hypertension could not be excluded.

The present study evaluated glucose tolerance before development of hypertension and found that relative glucose intolerance may precede the onset of this disorder. Women with insulin-dependent diabetes antedating pregnancy are known to have an increased risk of hypertensive phenomena;\textsuperscript{16} but these women primarily have insulin deficiency rather than insulin resistance and often have renal dysfunction that might underlie blood pressure elevation. More recently, risk of hypertension in pregnancy has been reported by some\textsuperscript{8,9} although not all\textsuperscript{17,18} investigators to be increased among women with gestational diabetes, a disorder associated with underlying insulin resistance.\textsuperscript{19} Some\textsuperscript{20,21} but not other\textsuperscript{6} studies have suggested a relation between less-striking degrees of glucose intolerance and subsequent hypertension in pregnancy.

In contrast to previous studies, the present study carefully excluded preexisting essential hypertension by documentation of normal blood pressures early in pregnancy or in the nonpregnant state. Although not uncommon during the reproductive years, essential hypertension is often undiagnosed in this population; many women do not routinely see a physician before pregnancy and may not receive obstetric care until the second trimester of pregnancy, when there is a normal physiological decrease in blood pressure. Confirmation of previous or subsequent normotension among women diagnosed with hypertension in pregnancy in the present study eliminates the possibility that the glucose intolerance noted in these women is explained by misclassification of women with preexisting essential hypertension.

We also distinguished between subtypes of hypertension in pregnancy and observed a significantly higher frequency of glucose intolerance (abnormal GLTs) only among women who developed transient hypertension. The increased incidence of later essential hypertension reported among women with transient hypertension\textsuperscript{10} but not preeclampsia\textsuperscript{10,22} is consistent with this observation.

In the present study significant associations were also noted between new-onset hypertension in pregnancy and prepregnancy BMI, weight gain during pregnancy, and blood pressures earlier in pregnancy. These observations are consistent with previously reported associations between hypertension in pregnancy and obesity,\textsuperscript{7} excessive pregnancy weight gain,\textsuperscript{23} and blood pressure in the second trimester\textsuperscript{24} or earlier.\textsuperscript{25} The greater weight gain noted among women who are subsequently diagnosed with preeclampsia may reflect early evidence of the edema characteristic of this disorder or, alternatively, could be pathogenic.

The observation of higher first-trimester blood pressures in initially normotensive women who subsequently develop transient hypertension suggests an underlying tendency to high blood pressure in these women that is unmasked or exaggerated by the pregnant state. Underlying essential hypertension is considered a risk factor for development of preeclampsia;\textsuperscript{26} our observation of higher baseline blood pressures among women developing this disorder indicates that relative increases in blood pressure within the normal range are also associated with increased risk.

Because of initial matching on age and race, no reliable assessment can be made of the effect of these factors on the risk of hypertension in pregnancy in our study population. Importantly, the relation between glucose tolerance and subsequent development of hypertension in pregnancy remained significant in our population after adjustment for maternal age, race, gestational age at GLT, and prepregnancy BMI.

The trend toward higher insulin levels in women who developed hypertension in pregnancy, although not statistically significant, nevertheless suggests a role for insulin resistance or hyperinsulinemia in the pathogenesis of this disorder. A link between insulin resistance and development of hypertension in pregnancy is also supported by the association of hypertension in pregnancy with increased BMI and excessive weight gain in this and other\textsuperscript{22} studies and with decreased physical activity in one report.\textsuperscript{27} Furthermore, a recent small study reporting higher glucose and insulin responses to
postpartum oral glucose load among African American women with a history of hypertension in pregnancy suggests that underlying insulin resistance may predispose to this disorder,²⁹ although these results will require confirmation in larger studies and other ethnic groups.

The failure to observe statistically significant differences in insulin levels might reflect the effect on insulin secretion of variable food intake at different times before GLT,²⁹ as this test was not routinely performed in the fasting state. Other researchers have demonstrated significantly higher insulin levels on GLT among nondiabetic women with high GLT glucose levels (≥7.8 mmol/L) than among those with lower glucose levels.³⁰ Measurement of glucose and insulin levels in response to standardized glucose challenge after a defined fast would provide a better assessment of insulin resistance in this population.

The explanation for the intermediate degree of glucose intolerance observed among women with preeclampsia remains uncertain. Preeclampsia may be a heterogeneous disorder, and insulin resistance may play a role in only some cases. Alternatively, because the definition of preeclampsia is made clinically, some women with this diagnosis may be misclassified; intermediate glucose intolerance in this group thus might reflect a combination of greater glucose intolerance among women with transient hypertension and more normal glucose intolerance among women with “true” preeclampsia. Some investigators consider primigravidity to be a criterion for the diagnosis of preeclampsia;²⁵ however, primigravidas in our study had glucose levels similar to those of other women diagnosed with preeclampsia.

In summary, our results indicate that glucose intolerance may be an important predictor of the development of new-onset hypertension in pregnancy, particularly transient hypertension. These data provide indirect support for the hypothesis that insulin resistance may have a role in the pathogenesis of hypertension in pregnancy.

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References
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