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.

Women who developed hypertension also had greater prepregnancy body mass index (P≤.0001) and baseline systolic and diastolic blood pressures (P≤.0001 for both), although all subjects were normotensive at baseline by study design. However, after adjustment for these and other potential confounders, an abnormal glucose loading test remained a significant predictor of development of hypertension (P<.05) and, specifically, nonproteinuric hypertension in pregnancy (P<.01). Among a subgroup of women in whom insulin levels were also measured (n=80), there was a nonsignificant trend toward higher insulin levels in women developing hypertension. These results suggest that relative glucose intolerance is associated with an increased risk of new-onset hypertension in pregnancy, particularly the nonproteinuric type, and indirectly support the hypothesis that insulin resistance may play a role in the pathogenesis of this disorder. (Hypertension. 1994;23[part 1]:717-721.)

Key Words  • glucose • hypertension, pregnancy-induced • pregnancy • preeclampsia

Essential 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
GLT indicates glucose loading test; BMI, body mass index; and BP, blood pressure. Values are mean (SD).
*Weight gain calculated from reported prepregnancy weight to GLT weight.
†P<.0001, ‡P<.01, hypertension in pregnancy vs normotensive.
§P<.001, ||P<.01, preeclampsia vs normotensive.
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<table>
<thead>
<tr>
<th>Hypertension in Pregnancy</th>
<th>Preeclampsia</th>
<th>Transient Hypertension</th>
<th>Normotensive</th>
</tr>
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<tbody>
<tr>
<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>
</tr>
<tr>
<td>Race, % white/Hispanic/black</td>
<td>76/8/15</td>
<td>70/10/20</td>
<td>83/6/11</td>
</tr>
<tr>
<td>First pregnancy, %</td>
<td>36</td>
<td>42</td>
<td>30</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>
</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>
</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>
</tr>
<tr>
<td>BP at baseline, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>115 (9)</td>
<td>115 (9)</td>
<td>115 (9)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>71 (7)</td>
<td>71 (7)</td>
<td>71 (6)</td>
</tr>
<tr>
<td>BP at GLT, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>120 (11)</td>
<td>121 (12)</td>
<td>119 (10)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73 (8)</td>
<td>73 (10)</td>
<td>73 (6)</td>
</tr>
</tbody>
</table>

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

†P<.0001, ‡P<.01, hypertension in pregnancy vs normotensive.
§P<.001, ||P<.01, preeclampsia vs normotensive.
<table>
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<tr>
<th>Demographic and Clinical Variables in Women Developing New-Onset Hypertension in Pregnancy, Either Preeclampsia or Transient Hypertension, and Women Remaining Normotensive to Term</th>
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</thead>
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<tr>
<td><strong>Hypertension in Pregnancy</strong> (n=97)</td>
</tr>
<tr>
<td>Age, y</td>
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<td>Race, % white/Hispanic/black</td>
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<tr>
<td>First pregnancy, %</td>
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To avoid inclusion of essential hypertensive women in the transient hypertensive or preeclamptic groups, we excluded women if they 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 who were lost to follow-up or did not attend screening tests were also excluded. Women who were lost to follow-up or did not attend screening tests were also excluded. Women who were lost to follow-up or did not attend screening tests were also excluded. Women who were lost to follow-up or did not attend screening tests were also excluded. Women who were lost to follow-up or did not attend screening tests were also excluded. Women who were lost to follow-up or did not attend screening tests were also excluded. Women who were lost to follow-up or did not attend screening tests were also excluded. Women who were lost to follow-up or did not attend screening tests were also excluded.

The study was approved by the Human Research Committee of Brigham and Women's Hospital.
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 ± 107 mm Hg) and DBP (71 ± 65 mm Hg) than women remaining normotensive to term (P < 0.001 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 < 0.001). At the time of GLT, women who developed hypertension also had significantly higher SBP (120 ± 110 mm Hg) and DBP (73 ± 66 mm Hg) than women who remained normotensive (P < 0.001 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 < 0.0001 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 < 0.01). 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 < 0.01). When hypertensive subgroups were examined separately, 36% of women developing transient hypertension had GLT glucose levels of 7.8 mmol/L or greater (P < 0.001 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 < 0.01). 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 < 0.05). 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 < 0.01) 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.

Fig 1. Bar graph shows glucose loading test results among women developing preeclampsia or transient hypertension and women remaining normotensive to term (mean±SEM). P < 0.025, transient hypertension vs normotensive.

Fig 2. Bar graph shows distribution of glucose loading test results among women developing preeclampsia or transient hypertension and women remaining normotensive to term. P < 0.0001, transient hypertension vs normotensive.
An association between insulin resistance and hypertension in pregnancy was initially suggested by reports of higher glucose levels on intravenous glucose tolerance testing, attenuated glucose response to intravenous insulin, and elevated insulin levels in response to a glucose load 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; 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 hypertension in pregnancy, but these women primarily have insulin deficiency rather than insulin resistance. Women with underlying essential hypertension is considered a risk factor for development of preeclampsia; however, this association is weak and blood pressures earlier in pregnancy. These observations are consistent with previously reported associations between hypertension in pregnancy and obesity, excessive pregnancy weight gain, and blood pressure in the second trimester or earlier. 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; 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 glucose loading test, and prepregnancy BMI.

TABLE 2. Crude and Adjusted Odds Ratio for New-Onset Hypertension in Pregnancy Associated With High Glucose Load Test (GLT) Glucose (≥7.8 mmol/L)

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude 3.7</td>
<td>1.5, 9.0</td>
</tr>
<tr>
<td>Adjusted for maternal age, gestational age at GLT, and race (white vs nonwhite) 3.5</td>
<td>1.4, 8.9</td>
</tr>
<tr>
<td>Adjusted also for prepregnant BMI 2.8</td>
<td>1.03, 7.6</td>
</tr>
</tbody>
</table>

GHT indicates glucose loading test; BMI, body mass Index.
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, 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, 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. 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 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; 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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