Pregnancy/Preeclampsia

Increased Sensitivity to Angiotensin II Is Present Postpartum in Women With a History of Hypertensive Pregnancy

Aditi R. Saxena, S. Ananth Karumanchi, Nancy J. Brown, Caroline M. Royle, Thomas F. McElrath, Ellen W. Seely

Abstract—Pregnancies complicated by new-onset hypertension are associated with increased sensitivity to angiotensin II, but it is unclear whether this sensitivity persists postpartum. We studied pressor response to infused angiotensin II in 25 normotensive postpartum women in both high- and low-sodium balance. Ten women had a history of hypertensive pregnancy (5 with preeclampsia; 5 with transient hypertension of pregnancy), and 15 women had a history of uncomplicated, normotensive pregnancy. Systolic and diastolic blood pressures, aldosterone, and soluble fms-like tyrosine kinase 1 levels were measured before and after angiotensin II infusion in both dietary phases. In high sodium balance, women with a history of hypertensive pregnancy were normotensive but had significantly higher systolic and diastolic blood pressures than controls (115 versus 104 mm Hg and 73 versus 65 mm Hg, respectively; P<0.05). Women with a history of hypertensive pregnancy had a pressor response to salt loading, demonstrated by an increase in systolic blood pressure on a high-salt diet. They also had greater systolic pressor response (10 versus 2 mm Hg; P=0.03), greater increase in aldosterone (56.8 versus 30.8 ng/dL; P=0.03), and increase in soluble fms-like tyrosine kinase 1 levels (11.0 versus 18.9 pg/mL; P=0.02) after infusion of angiotensin II in low-sodium balance compared with controls. Thus, women with a history of hypertensive pregnancy demonstrated salt sensitivity of blood pressure and had increased pressor, adrenal, and soluble fms-like tyrosine kinase 1 responses to infused angiotensin II in low-sodium balance. Increased sensitivity to angiotensin II observed during pregnancy in women with hypertensive pregnancy is present postpartum; this feature may contribute to future cardiovascular risk in these women. (Hypertension. 2010;55:1239-1245.)

Key Words: preeclampsia  •  pregnancy-induced hypertension  •  renin-angiotensin system  •  postpartum  •  sFlt-1

Approximately 5% to 10% of pregnancies are complicated by new-onset hypertension, resulting in significant morbidity and mortality for both the mother and the neonate.1 Several studies have shown that women who develop elevated blood pressure during pregnancy, in the absence of underlying chronic essential hypertension, return to a normotensive state postpartum but appear to have an increased risk of cardiovascular disease later in life.2–6 This observation suggests that there may be abnormalities in vascular function that persist postpartum, predisposing these women to future development of cardiovascular disease.7

Normal pregnancy has been identified as a state of relative resistance to the pressor effects of angiotensin II (Ang II).8,9 In contrast, pregnant women with new-onset hypertension demonstrate increased sensitivity to the pressor effects of Ang II, even before the onset of hypertension.10 These women return to a normotensive state postpartum, but whether sensitivity to Ang II also normalizes postpartum has not been well explored.

Methods

Study Population

Twenty-five healthy normotensive postpartum women were studied at 2 sites, Brigham and Women’s Hospital in Boston or Vanderbilt Medical Center in Nashville. The institutional review committees at both hospitals approved the study protocol, and all of the women provided written, informed consent before participating in the study. All of the women met the inclusion criteria of no history of gestational or nongestational diabetes mellitus, no history of hypertension before or after pregnancy, and no other current medical illness. Ten of these women had a history of new-onset hypertension in pregnancy and were diagnosed with either preeclampsia or transient hypertension of pregnancy (THP).1 These women were normotensive before pregnancy and normotensive postpartum and were confirmed to have a history of new-onset hypertension in pregnancy if they had a documented blood pressure of ≥140/90 mm Hg on ≥2 occasions ≥6 hours apart during the third trimester of pregnancy.1 Five women met criteria for preeclampsia with proteinuria (either by a 24-hour urine sample with ≥300 mg of protein per day or urine dipstick with ≥2+ protein). In addition, 5 other subjects met blood pressure criteria without proteinuria and

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were determined to have had THP. The remaining 15 women had a history of normotensive pregnancy. Blood pressure and urine protein excretion during pregnancy for women with a history of new-onset hypertension in pregnancy were confirmed by investigator review of the medical charts. No subjects were taking prescription medications, oral contraceptives, or hormone therapy at the time of study.

Ang II Infusion

Ang II infusions were performed after subjects ingested a standardized isocaloric high-salt diet containing 250 mEq of sodium and 100 mEq of potassium for 1 week. Subjects underwent a second Ang II infusion after completing a low-salt diet for 1 week, which contained 10 mEq of sodium and 100 mEq of potassium. Two women with THP and 1 woman with preeclampsia did not complete the low-salt phase of the study. Subjects were determined to be in sodium balance on the day before the Ang II infusion on both high- and low-salt diets by measuring 24-hour urinary excretion of sodium. Sodium balance was defined as urinary sodium ≥200 mmol on the high-salt diet and ≤20 mmol on the low-salt diet. Subjects arrived at the General Clinical Research Center on the morning of day 8, after completing 7 days of the high-salt diet. An intravenous catheter was placed in each arm; one was used for phlebotomy, whereas the other was used for infusion. Each subject received an infusion of Ang II amide (CIBA-Geigy) at 3 ng/kg per minute for 45 minutes delivered by an electronic infusion pump (Baxter Corp). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were monitored every 2 minutes during the Ang II infusion using a Dinamap automated blood pressure monitor (Critikon, Inc). In addition, blood was drawn for the measurement of aldosterone, plasma renin activity (PRA), and cortisol both before and after administration of Ang II. Subjects then ingested a low-salt diet for 7 days, after which they were readmitted to the General Clinical Research Center and again underwent the Ang II infusion protocol described above.

Laboratory Assays

Blood samples were collected on ice and centrifuged in a refrigerated centrifuge. Plasma and urinary sodium levels were measured using autoanalyzer techniques. Aldosterone, PRA, and cortisol levels were measured using radioimmunoassay techniques as described previously. Measurements of angiogenic factors, including soluble fms-like tyrosine kinase 1 (sFlt-1), placental growth factor, and soluble endoglin, were performed on a subset of subjects. Samples for these analyses were stored at −80°C and thawed only for current studies. A commercial ELISA kit was used for measurement of sFlt-1, placental growth factor, and soluble endoglin (R&D Systems). The interassay coefficients of variation were 13%, 5%, and 12% for sFlt-1, placental growth factor, and soluble endoglin, respectively.

Statistical Analysis

Changes in SBP and DBP were calculated before and after administration of Ang II in both the low- and high-sodium balance. In addition, mean differences in aldosterone, cortisol, PRA, and levels of angiogenic factors were also calculated before and after Ang II infusions. Salt sensitivity was determined by subtracting baseline blood pressures in low-sodium balance from baseline blood pressures in high-sodium balance. The Shapiro-Wilk test was used to test for normal distribution. There were no significant differences in any of the blood pressure or hormonal measurements between women with a history of THP and those with a history of preeclampsia (data not shown), so these 2 subsets were combined and studied as one group. For data that were normally distributed, the paired t-test was used to perform 2-group comparisons of responses to Ang II between women with a history of normotensive pregnancy and those with a history of new-onset hypertension in pregnancy. For nonnormally distributed data, the Wilcoxon rank-sum test was used. Data are expressed as mean±SEM. A P value of <0.05 was considered significant.

### Table 1. Characteristics of Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>History of Normotensive Pregnancy (n=15)</th>
<th>History of New-Onset Hypertension in Pregnancy (n=10)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>30.9±0.9</td>
<td>30.3±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>13 (87)</td>
<td>9 (90)</td>
<td></td>
</tr>
<tr>
<td>Blacks</td>
<td>2 (13)</td>
<td>1 (10)</td>
<td></td>
</tr>
<tr>
<td>Gravidity</td>
<td>1.3±0.1</td>
<td>2.3±0.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Parity</td>
<td>1.3±0.1</td>
<td>1.4±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69.7±3.2</td>
<td>68.3±5.5</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.3±1.1</td>
<td>26.7±2.0</td>
<td>NS</td>
</tr>
<tr>
<td>High-salt urinary sodium, mmol/24 h</td>
<td>208±16</td>
<td>208±5</td>
<td>NS</td>
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<tr>
<td>Low-salt urinary sodium, mmol/24 h</td>
<td>10±3</td>
<td>20±6</td>
<td>NS</td>
</tr>
</tbody>
</table>

*For the history of new-onset hypertension in pregnancy group, n=7 for the low-salt phase, because 3 subjects did not complete this phase.

Results

Subject Demographics

All of the subjects were ≥8 months postpartum at the time of study, and none were lactating at the time of study. The majority of women in both groups were white, and there were no significant differences in age, weight, body mass index, or urinary sodium levels between the groups (Table 1). Although the 2 groups differed in gravidity, there were no significant differences in parity (Table 1). We compared differences within baseline blood pressures and hormone levels and responses of these parameters to Ang II and found no differences between women with gravidity ≤2 and women with gravidity >2 (data not shown). In addition, women with a history of normotensive pregnancy had a median postpartum time of 21 months from pregnancy, whereas women with a history of new-onset hypertension in pregnancy had a median postpartum duration of 13 months. There were no significant differences between the 2 groups with respect to the time from pregnancy. As described previously, women with a history of new-onset hypertension in pregnancy consisted of 5 women with a history of preeclampsia and 5 women with a history of THP.

Blood Pressure Response to Dietary Salt

Baseline Blood Pressure Measurements

Both groups had baseline SBP and DBP in the normotensive range in both high- and low-sodium balance. Women with a history of new-onset hypertension in pregnancy, however, had significantly higher baseline blood pressures after ingesting the high-salt diet compared with women with a history of normotensive pregnancy. In addition, women with a history of new-onset hypertension in pregnancy had significantly higher baseline DBP after ingesting the low-salt diet (Table 2).
Hormone Response to Dietary Salt

No significant differences were detected in baseline aldosterone, PRA, or cortisol in either a low- or high-sodium balance compared with those with a history of new-onset hypertension in pregnancy and with those with a history of normotensive pregnancy (Table 3). Both groups demonstrated similar increases in aldosterone after ingesting the low-salt diet compared with the high-salt diet.

<table>
<thead>
<tr>
<th>Hormones</th>
<th>History of Normotensive Pregnancy (n=15)</th>
<th>History of New-Onset Hypertension in Pregnancy (n=10)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline aldosterone, ng/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High salt</td>
<td>3.9±0.4</td>
<td>3.8±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Low salt</td>
<td>20.0±2.7</td>
<td>19.3±4.3</td>
<td>NS</td>
</tr>
<tr>
<td>∆ aldosterone</td>
<td>16.1±2.8</td>
<td>15.3±4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline PRA, ng/mL per h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High salt</td>
<td>0.7±0.1</td>
<td>0.7±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Low salt</td>
<td>3.2±0.5</td>
<td>3.0±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>∆ PRA</td>
<td>2.6±0.5</td>
<td>2.2±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline cortisol, μg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High salt</td>
<td>9.4±1.1</td>
<td>7.7±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Low salt</td>
<td>11.7±2.5</td>
<td>9.0±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>∆ cortisol</td>
<td>2.3±1.7</td>
<td>1.4±0.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

*For the history of new-onset hypertension in pregnancy group, n=7 for the low-salt phase. NS indicates not significant; ∆, change in hormone level calculated between low-salt and high-salt diets.

Sensitivity of Blood Pressure to Salt Intake

Compared with women with a history of normotensive pregnancy, women with a history of new-onset hypertension in pregnancy demonstrated a significantly greater rise in SBP (P=0.03) with an increase in sodium intake in the high-sodium balance (4 versus 1 mm Hg; Table 2). The difference in DBP between the high- and low-sodium balance was not significantly different between the 2 groups.

Blood Pressure Response to Ang II

Women with a history of normotensive pregnancy modulated their response to Ang II on the basis of sodium intake. They demonstrated a smaller systolic pressor response to Ang II in the low-sodium balance compared with high-sodium balance (2 versus 10 mm Hg, respectively; P<0.01; Figure 1). In contrast, women with a history of new-onset hypertension in pregnancy did not modulate response to Ang II on the basis of sodium intake; they had similar pressor responses to Ang II after ingesting both high- and low-salt diets (11 versus 10 mm Hg; P=0.7; Figure 1). Furthermore, the women with...
a history of new-onset hypertension in pregnancy had a significantly greater systolic pressor response to Ang II in the low-sodium balance compared with women with a history of normotensive pregnancy (10 versus 2 mm Hg, respectively; \( P = 0.03 \); Figure 1). There were no significant differences in responses of SBP in high-sodium balance (10 versus 11 mm Hg) in women with a history of normotensive pregnancy and women with a history of new-onset hypertension in pregnancy, respectively. Furthermore, there were no differences in DBP between the women with a history of normotensive pregnancy versus women with a history of new-onset hypertension in pregnancy (6 versus 8 mm Hg, respectively) in low-sodium balance.

**Hormone Response to Ang II**

Aldosterone response to infused Ang II was similar between the 2 groups in high-sodium balance (Table 4). However, women with a history of new-onset hypertension in pregnancy had a significantly greater aldosterone response in low-sodium balance than women with a history of normotensive pregnancy (56.8 versus 30.8 ng/dL, respectively; \( P = 0.03 \); Table 4). No differences were found between the 2 groups in high sodium balance. In addition, the responses of PRA and cortisol to Ang II were not different between the 2 groups on either diet.

**sFlt-1 Response to Ang II**

In high-sodium balance, post-Ang II sFlt-1 levels were not significantly different between women with a history of normotensive pregnancy and those with a history of new-onset hypertension in pregnancy with mean levels of 19.3±5.8 and 10.4±4.8 pg/mL, respectively. In addition, the change in sFlt-1 before and after infused Ang II also was not significantly different between the 2 groups in high-sodium balance.

In low-sodium balance in women with a history of normotensive pregnancy, sFlt-1 decreased to 11.3±4.4 pg/mL after Ang II infusion. In contrast, in women with a history of new-onset hypertension in pregnancy, sFlt-1 levels increased to 35.2±8.3 pg/mL. Levels of stimulated sFlt-1 differed significantly between these groups (\( P = 0.02 \)). Furthermore, the change in sFlt-1 after Ang II infusion was significantly different between the 2 study groups (Figure 2). Stimulated levels of soluble endoglin did not differ significantly between women with a history of normotensive pregnancy and women with a history of new-onset hypertension in pregnancy in either high-sodium balance (3.7±0.2 versus 3.8±0.5 ng/mL, respectively) or low-sodium balance (3.6±0.2 versus 3.7±0.5 ng/mL, respectively).

**Discussion**

Women with a history of new-onset hypertension in pregnancy demonstrated significantly higher baseline blood pressures compared with women with a history of normotensive pregnancy, as reported previously, although all of the baseline blood pressures were within the normotensive range. This finding was observed in both high- and low-sodium balance. Of note, women with a history of new-onset hypertension in pregnancy demonstrated increased vascular and adrenal responsiveness to Ang II, manifested by a greater pressor and aldosterone response to infused Ang II compared with Ang II in low-sodium balance. Furthermore, sFlt-1 levels in these women also increased significantly in response to Ang II in low-sodium balance.

This study demonstrates that women with a history of new-onset hypertension in pregnancy are more salt sensitive than their counterparts, as demonstrated by a greater systolic pressor response to high-sodium intake. In addition, women with a history of new-onset hypertension in pregnancy are not able to change their response to infused Ang II.
Ang II on the basis of sodium intake. Instead, they demonstrate similar sensitivity to infused Ang II on both high- and low-salt diets. This finding contrasts sharply with women with a history of normotensive pregnancy who were able to modulate blood pressure response to Ang II on the basis of sodium intake. Our study indicates that increased sensitivity to infused Ang II that has been identified during pregnancies complicated by new-onset hypertension does indeed exist postpartum.

Salt sensitivity is defined as the inability to excrete a sodium load without increasing blood pressure and is a feature of many hypertensive populations. In our study, women with a history of normotensive pregnancy were able to maintain high sodium balance without increasing their blood pressure. In contrast, women with a history of new-onset hypertension in pregnancy demonstrated a significant rise in blood pressure with increased sodium intake, although their blood pressures were maintained within the normotensive range. Several features have been associated with salt-sensitive hypertension, including insulin resistance, which has also been associated separately with new-onset hypertension in pregnancy.

Sodium intake has major effects on the renin-angiotensin system, and healthy, normotensive individuals are able to modulate their pressor response to infused Ang II on the basis of sodium intake. In low-sodium balance, the renin-angiotensin system is maximally stimulated, and the pressor response to infused Ang II is typically blunted compared with a high-sodium balance. However, in our study, the postpartum new-onset hypertension in the pregnancy population did not change response to infused Ang II with varying sodium intake. Their sensitivity to infused Ang II was increased in both high- and low-sodium balance. A previous study, conducted on a single and intermediate standardized sodium diet (100 mEq of sodium) did not detect differences in sensitivity to infused Ang II between women with a history of new-onset hypertension in pregnancy and normotensive pregnancies. Our study did not demonstrate significant differences between the 2 study groups on the high-sodium balance. It is likely that a moderate or high level of sodium intake does not distinguish between the new-onset hypertension in pregnancy and the normotensive groups. Differentiation between the groups may only be possible at very low sodium intake. In addition, distinction between the normotensive and new-onset hypertension in pregnancy populations may only be observed by comparing responses to Ang II between high- and low-sodium intakes, as we have demonstrated here. In addition, the previous study was conducted with lower doses of infused Ang II, which also may not have allowed for distinction between the 2 groups.

Of interest, we also saw an increased aldosterone response to Ang II in the low-sodium balance, which indicates an increased responsiveness to Ang II in the adrenal glands, in addition to the increased vascular responsiveness described above. Increased aldosterone levels were observed after Ang II infusions but were not accompanied by significant increases in cortisol, indicating that the enhanced responsiveness was specific to Ang II and was not driven by overall adrenal stimulation through another mediator, such as adrenocorticotropic hormone.

sFlt-1 has been studied extensively in the preeclampsia population and has also been shown to persist in the postpartum state. There is controversy as to whether sFlt-1 remains elevated postpartum in pregnancies complicated by preeclampsia. In one study, mean levels of sFlt-1 were significantly higher in women with a history of preeclampsia when studied 8 to 28 months postpartum, with mean levels of $41.6 \pm 6.7$ pg/mL. In contrast, another study showed no differences in sFlt-1 levels in women with previous preeclampsia compared with women with previous normotensive pregnancy. In our study populations, there were no significant differences in baseline sFlt-1 levels in either high- or low-sodium balance; however, our case and control populations were smaller than either of those 2 studies.

The link between sFlt-1 and infused Ang II is particularly interesting, because pregnant mouse models have shown that infused Ang II regulates sFlt-1 production via activation of the Ang II type 1 (AT$_1$) receptor. Our study examines sFlt-1 response to infused Ang II in human subjects. There were no significant differences in post-Ang II sFlt-1 levels between the 2 study groups in high-sodium balance. However, women with a history of new-onset hypertension in pregnancy demonstrated significantly increased sFlt-1 levels in response to infused Ang II in low-sodium balance compared with women with history of normotensive pregnancy. Analogous to the other physiological changes seen in low-sodium balance in women with a history of new-onset hypertension, Ang II stimulated significant increases in sFlt-1 levels under these conditions as well. The specificity of this response was bolstered further by the lack of a similar response in soluble endoglin, another angiogenic factor that has been studied in relation to preeclampsia.

Our case and control populations did not differ significantly with respect to demographic characteristics. As a result, it is unlikely that these factors affected the response to infused Ang II. Women with a history of new-onset hypertension in pregnancy did have higher gravidity compared with their counterparts. However, several studies have explored the relationship between abortion and miscarriage with preeclampsia, and a large population-based study found no increased risk of preeclampsia in women with history of a previous therapeutic or spontaneous abortion. In addition, we compared differences within baseline blood pressures and hormone levels and responses of these parameters to Ang II and found no difference between women with lower gravidity and women with higher gravidity. We did not have data on the phase of the menstrual cycle in which these subjects were studied. A previous study studied pressor response to Ang II across the menstrual cycle and did not demonstrate differences in response between follicular and luteal phases. Because the protocols were performed identically in the case and control populations, we have no reason to believe that differences in the menstrual cycle phase would have contributed to the differences in Ang II sensitivity observed in this study.
Our study has several strengths. All of the pregnancies were well characterized, and all of the diagnoses were confirmed by investigator review of medical charts. In addition, the subjects received Ang II infusions on 2 different sodium intakes, which allowed for comparisons of Ang II responsiveness. All of the subjects were confirmed to be in salt balance, which is extremely important, because standardization of sodium levels is integral for the analysis of renin-angiotensin system activity.

We acknowledge, however, that the study has some limitations. The number of subjects studied was small, because enrollment was affected by the length and detailed structure of the study protocol, which required 2 weeks of standardized sodium intake and 24-hour urine collections to confirm salt balance. In addition, most subjects in the study were white. Despite a small sample size, however, significant differences were observed between the 2 study populations. A future study in a larger, more diverse population would be of interest to confirm these findings. Another potential limitation was the heterogeneity of the new-onset hypertension in the pregnancy group, half of whom had been diagnosed with preeclampsia and half of whom had THP. When we performed analyses of the THP and preeclampsia subsets, they did not appear to differ significantly in their blood pressure or hormonal responses to dietary sodium or Ang II. However, we acknowledge that our ability to detect any differences may be affected by small sample size within each subset. In the seminal work in 1973 by Gant et al., which demonstrated that increased pressor response to Ang II precedes the onset of hypertension in new-onset hypertension in pregnancy, both preeclamptic and gestational hypertensive women were studied together. As a result, the characteristics of our population are similar to those presented in the original article by Gant et al. Furthermore, in the population-based studies that have reported long-term outcomes in women with hypertensive pregnancies, the distinction between THP and preeclampsia is often not apparent, because this distinction can only really be made with quantification of urinary protein excretion, which typically is not available in retrospective studies.

The increased sensitivity to infused Ang II observed in women with a history of new-onset hypertension suggests increased expression or activity of the AT₁ receptor. Increased AT₁ receptor expression has been reported in placental tissue of preeclamptic pregnancies. In addition, AT₁ autoantibodies have been characterized in the preeclamptic population and have also been shown to persist in the postpartum state. It would be interesting to characterize the relationship between AT₁ autoantibodies and sensitivity to infused Ang II in the postpartum new-onset hypertension in pregnancy population. Theoretically, we would expect that the presence of agonistic AT₁ autoantibodies would result in downregulation of AT₁ receptor expression, which, in turn, should decrease sensitivity to infused Ang II, which was not demonstrated in our study. However, the relationship is likely more complex.

**Perspectives**

This study demonstrates that increased sensitivity to infused Ang II exists in the postpartum state in women with a history of new-onset hypertension in pregnancy. This increased sensitivity to Ang II is present in the vasculature and in the adrenal glands, with a suggestion of sFlt-1 responsiveness. In addition, women with a history of new-onset hypertension in pregnancy are unable to modulate a response to infused Ang II on the basis of salt intake. These abnormalities suggest a dysregulation of the renin-angiotensin system in this population, which, in turn, could be related to the increased long-term cardiovascular risk observed in women with a history of new-onset hypertension in pregnancy.

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**Disclosures**

None.

**References**


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