Renal Effects of Angiotensin II Infusions in Normotensive Pregnant and Nonpregnant Women

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Infusion of angiotensin II has profound effects upon renal function in normotensive subjects. The glomerular filtration rate and renal plasma flow are reduced and filtration fraction rises; there is a marked decrease in urine volume and in excretion of sodium, potassium, and chloride.1-4 Although angiotensin II is the most potent pressor substance known, doses even too small to raise the blood pressure will elicit the renal changes.5 The promptness of the renal response and its occurrence in adrenalectomized subjects6 suggest that angiotensin has a direct effect upon the kidney in causing sodium retention. Recent evidence indicates, furthermore, that the renin-angiotensin system may be a major humoral regulator of aldosterone secretion,7-14 which would in turn have a bearing upon sodium retention.

Jones et al.15 found the average rate of aldosterone secretion in six pregnant women to be about three times that in six nonpregnant women. This has been confirmed16 and extended17 by work thus far published only in abstracts. It is not known that angiotensin mediates this great increase, but it has been suggested that pregnant women may inactivate exogenous angiotensin at an accelerated rate. Abdul-Karim and Assali18 found smaller pressor responses to single injections of 5 μg of synthetic angiotensin II in pregnant than in nonpregnant women, and related the observation to Page's19 report of a progressive rise in plasma angiotensinase during human pregnancy.

The foregoing considerations prompted us to study the renal effects of angiotensin II infusions in pregnant and nonpregnant normotensive women.

Methods

Ten normotensive nonpregnant women on the gynecologic wards were used as a control series. All were of child-bearing age, afebrile and free of recognized extrapelvic disease. Two groups of normotensive pregnant women were studied: (a) ten near term (38 to 42 weeks' gestation), and (b) ten in the 26th to 35th weeks of gestation. Many of these patients were admitted from the clinic specifically for the study; others had been admitted because of false labor or premature rupture of the membranes, or for elective Cesarean section. The patients, with few exceptions, were studied on the first or second day in the hospital because the hospital diet of all antepartum patients provides a daily intake of only 30 mEq of sodium.

The patients usually fasted overnight and forced fluids for two to three hours before the tests, which began at about 9 AM. A multiple-eyed catheter was usually placed in the bladder but in four cases urine was collected directly from the ureters.* Priming doses of 10% inulin and, in ten cases, 20% sodium para-aminobenzenesulfonate (PAH) were injected intravenously; sustaining infusions of 1% inulin and, in ten cases, 0.57% PAH were given at a rate of 3.7 ml per minute, with a Bowman pump. When PAH was given, it was diluted in 0.9% sodium chloride; in all other cases, the sustaining infusion of inulin was given in 5% dextrose, because the saline infusions resulted in steadily increasing excretion rates of sodium and chloride during the control periods. After a minimum of 60 minutes for equilibration, the clearance periods began; they varied from 15 to 50 minutes, depending upon the volume of urine output. The bladder was washed out at least

*The ureteral catheterizations were done for us by Gerald M. Litzky of the Urology Department.

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twice, with about 30 ml of water and 40 cc of air, at each urine collection. Blood samples were taken four to five minutes before the midpoint of each clearance period. After three control periods angiotensin \( \text{II}^* \) was infused at a rate of 0.5 \( \mu \text{g/min} \), beginning four to five minutes before the last control urine was taken and continuing until the end of the fifth clearance period (second period during the angiotensin \( \text{II} \) infusion, which lasted 45 to 90 minutes). When sixth, and sometimes seventh, (post-infusion) periods were included in the test, the angiotensin \( \text{II} \) infusion was discontinued about five minutes before the end of the fifth period.

Serum inulins were measured in each of duplicate protein-free filtrates and urine inulins were measured in duplicate, by the method of Roe, Epstein, and Goldstein.\(^{20}\) Urinary chlorides were titrated by the method of Volhard and Harvey.\(^{21}\) Sodium was measured with a Perkin-Elmer 52C flame photometer, using an internal lithium standard, \( \text{PAH} \) in serum and urine was measured in duplicate by the method of Smith et al.\(^{22}\) Blood pressures were estimated with a sphygmomanometer.

**Results**

**NONPREGNANT NORMOTENSIVE WOMEN**

In accord with the reports of others,\(^1\)-\(^7\) the infusion of angiotensin in nonpregnant normotensive subjects markedly reduced urine volume and the outputs of sodium and chloride. The volume of urine output fell from control levels by an average of 74% in the first period of angiotensin \( \text{II} \) infusion and by 83% in the second period. Sodium excretion diminished 74% and 72% and chloride excretion 66% and 67% in the first and second periods, respectively. The percentage changes in water and sodium excretion are shown in figure 1. Control values usually represent the averages of three consistent clearance periods; whenever the control values fluctuated, as during saline infusion, the last control period was used.

The inulin clearances fell during angiotensin \( \text{II} \) infusion in every case; the average decrease was 26% in the first period of infusion and 21% in the second. The serum inulin concentrations, which had been essentially constant during the control periods, rose in every case; the increases varied from 2% to 10% and averaged 5%. \( \text{PAH} \) clearances were done in only three cases; the decreases were more marked than those in the inulin clearances, with consequent increases in the filtration fractions.

The blood pressure rose an average of 31 mm Hg systolic and 27 mm Hg diastolic in the first period of angiotensin \( \text{II} \) infusion. In the second period, the increments over control levels were 27 and 21 mm Hg, respectively.

**NORMOTENSIVE PREGNANT WOMEN NEAR TERM**

The effects of angiotensin \( \text{II} \) infusions in women at the end of normal pregnancies were strikingly less than in nonpregnant normotensive women in respect to water, sodium, and chloride excretions and in pressor response. The volume of urine output fell an average of only 23% in the first period and 41% in the second period of angiotensin \( \text{II} \) infusion. The decreases in sodium excretion averaged 41% and 47%, respectively, and in chloride excretion the decrements averaged 43% and 47%, respectively. The mean blood pressure increase was 21/15 mm Hg in systolic/diastolic pressures in the first period; in nine of the ten patients the blood pressure fell slowly during the second period of angiotensin \( \text{II} \) infusion and by the end averaged only 9/9 mm above control levels, for all subjects.

The decreases in inulin clearance were sim-
FIGURE 2

Normotensive pregnant women near term. Percentage changes from control levels in urine volume output (open bars) and sodium excretion (solid bars) in two successive clearance periods during the infusion of angiotensin II, 0.5 μg/min.

Similar to those seen in nonpregnant normotensive women, averaging 22% in the first period and 28% in the second period of angiotensin II infusion. The mean increase in serum insulin concentration in the first period was only 1%, and only six of the ten had increases. This would suggest that the apparent decreases in clearance had been exaggerated by dead space error. The filtration fraction rose in all four cases in which the PAH clearance was measured.

The percentage changes in water and sodium excretions are depicted in figure 2, where it may be seen that the urine volume output actually increased in two subjects.

NORMOTENSIVE WOMEN IN THE 26TH TO 35TH WEEKS OF PREGNANCY

Some of the major hemodynamic changes of pregnancy, such as the increases in cardiac output and renal blood flow, largely disappear as term is approached. It is therefore of interest to compare the renal effects of angiotensin II in women near term with those in women at an earlier stage of pregnancy, when these physiological changes are at or near their maxima.

The data in figure 3 indicate that in some respects infusions of angiotensin II had less effect at this stage of pregnancy than at term. The decrease in the volume of urine output averaged about the same as at term, but the sodium excretion fell an average of only 16% in the first period and 3% in the second period of angiotensin II infusion. Sodium excretion actually increased in two patients and did not change at all in another two. The pattern of chloride excretion usually followed that of sodium excretion but in the second period of infusion the mean change from control levels was +10%.

The average decreases in insulin clearance were less marked than in the other groups of women, averaging 16% in the first period and 8% in the second period of angiotensin II infusion. On the average, the serum insulin concentration did not increase in the first period, although small increases were seen in half the cases. PAH clearances were done in only three cases; there was no change in one, a transitory drop in one, and a marked increase during the second period of angiotensin II infusion in the third. The filtration fraction fell in this last case and increased only slightly in the other two.

The blood pressure rise in the first period of infusion averaged 15/13 mm Hg in the systolic/diastolic readings. In eight of the ten cases, the blood pressure fell slowly during the second period of infusion; near the end of the angiotensin infusion the blood pressure averaged only 6 mm Hg systolic and 7 mm Hg diastolic above control levels.

Table 1 shows a sample case* from each of the three groups of women; none is typical in all respects, because of the variability in the several factors recorded.

STATISTICAL ANALYSIS

Table 2 shows the average changes from control levels for the inulin clearances, urine volumes, and excretions of sodium and chloride in the three groups of women. The statistical significance of the differences was assessed by Student's t-test, and the table shows the results of this analysis. The effect of

*Detailed tabular data summarizing results from each experiment have been deposited as Document No. 7522 with ADI Auxiliary Publications Project, Photoduplication Service, Washington 25, D. C. A copy may be obtained by citing the Document number and by remitting $1.25 for a photoprint or for 35 mm microfilm. Make checks or money orders payable to Chief, Photoduplication Service, Library of Congress.
Angiotensin II upon the inulin clearance was not significantly different in the various groups. The effect upon the volume of urine output was significantly less in the two groups of pregnant women than in the nonpregnant women, but pregnant women at term did not differ from those in earlier pregnancy. With respect to sodium and chloride excretion rates, there were significant differences from group to group, in that angiotensin II had less effect in women 26 to 35 weeks pregnant than in women at term, who in turn showed less effect than did nonpregnant women.

Statistical analyses of blood pressure responses are not shown in the table, but the systolic and diastolic blood pressure rises in the pregnant women of both groups were significantly less than those in nonpregnant women, with one exception. In the first period of angiotensin II infusion in pregnant women at term, the average rise of 21 mm Hg in the systolic pressure was not different from the average rise of 31 mm Hg seen in nonpregnant women \((t = 2.02, P > 0.05)\). There was no significant difference between the pressor responses of the two groups of pregnant women.

**Discussion**

Average excretions of sodium and chloride in the control periods were highest in the nonpregnant subjects, intermediate in pregnant women at term, and lowest in women in the 26th to 35th weeks of pregnancy. This observation raised the possibility that the percentage changes in rates of electrolyte excretion might be less in each of these successive groups because the decreases to a common minimum would be successively less. Analysis shows that this possibility does not seem to be the explanation for the lesser response of the pregnant women. Six pregnant women excreted 92 to 140 (average 117) \(\mu\)Eq of sodium per minute in the control periods. Excluding all nonpregnant women who excreted more than 150 \(\mu\)Eq per minute, the remaining six excreted 54 to 148 (average 99) \(\mu\)Eq. In the pregnant women, the mean decrease in sodium excretion was 28% in both the first and second periods of angiotensin infusion;

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**FIGURE 3**

Normotensive women in the 26th to 35th weeks of gestation. Percentage changes from control levels in urine volume output (open bars) and sodium excretion (solid bars) in two successive clearance periods during the infusion of angiotensin II, 0.5 \(\mu\)g/min.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Pregnancy status</th>
<th>Clearance periods*</th>
<th>Inulin clearance ml/min</th>
<th>Approximate urine volume ml/min</th>
<th>Sodium excretion (\mu)Eq/min</th>
<th>Chloride excretion (\mu)Eq/min</th>
<th>Blood pressure increase mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpregnant</td>
<td>Control</td>
<td>108</td>
<td>7.7</td>
<td>54</td>
<td>50</td>
<td>27/18</td>
</tr>
<tr>
<td></td>
<td>Period 1</td>
<td>81</td>
<td>0.5</td>
<td>10</td>
<td>17</td>
<td>27/18</td>
</tr>
<tr>
<td></td>
<td>Period 2</td>
<td>89</td>
<td>0.4</td>
<td>12</td>
<td>20</td>
<td>27/18</td>
</tr>
<tr>
<td></td>
<td>Post Inf.</td>
<td>104</td>
<td>0.8</td>
<td>27</td>
<td>45</td>
<td>27/18</td>
</tr>
<tr>
<td>At term</td>
<td>Control</td>
<td>164</td>
<td>3.3</td>
<td>41</td>
<td>52</td>
<td>6/8</td>
</tr>
<tr>
<td></td>
<td>Period 1</td>
<td>119</td>
<td>1.9</td>
<td>17</td>
<td>32</td>
<td>5/2</td>
</tr>
<tr>
<td></td>
<td>Period 2</td>
<td>135</td>
<td>1.6</td>
<td>14</td>
<td>34</td>
<td>5/2</td>
</tr>
<tr>
<td></td>
<td>Post Inf.</td>
<td>143</td>
<td>5.1</td>
<td>29</td>
<td>32</td>
<td>20/12</td>
</tr>
</tbody>
</table>

60 weeks

|                 | Control            | 137                     | 6.8                           | 31                            | 28                            | 34/29                         |
|                 | Period 1           | 113                     | 4.4                           | 23                            | 28                            | 34/29                         |
|                 | Period 2           | 143                     | 5.1                           | 29                            | 32                            | 20/12                         |
|                 | Post Inf.          | 120                     | 6.1                           | 49                            | 44                            | 20/12                         |

*Control periods are the averages of three observations except when the urine volume or electrolyte excretion rates were changing significantly, in which case the last of the three control periods is shown for these factors.
TABLE 2
Renal Effects of Angiotensin \(\text{II}\) Infusion, 0.5 \(\mu\)g/min in Nonpregnant and Pregnant Normotensive Women

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Inulin clearance</th>
<th>Urine volume</th>
<th>Sodium excretion</th>
<th>Chloride excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Period 1</td>
<td>Period 2</td>
<td>Period 1</td>
<td>Period 2</td>
</tr>
<tr>
<td>Nonpregnant</td>
<td>10</td>
<td>-26</td>
<td>-21</td>
<td>-74</td>
<td>-83</td>
</tr>
<tr>
<td>Pregnant, near term</td>
<td>10</td>
<td>-22</td>
<td>-28</td>
<td>-74</td>
<td>-83</td>
</tr>
<tr>
<td>Pregnant, 26 to 35 weeks</td>
<td>10</td>
<td>-16</td>
<td>-8</td>
<td>-36</td>
<td>-49</td>
</tr>
<tr>
<td>Term pregnant vs. nonpregnant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(t)</td>
<td></td>
<td>&gt;0.1</td>
<td>&gt;0.1</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Term pregnant vs. 26 to 35 weeks pregnant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(t)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 to 35 weeks pregnant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonpregnant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(t)</td>
<td></td>
<td>&gt;0.5</td>
<td>&gt;0.1</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

The corresponding decreases in the nonpregnant women were 71% and 69%, respectively. The effect of angiotensin \(\text{II}\) in depressing sodium excretion was significantly less in the pregnant women \((P < 0.01)\).

Average control urine volume was higher in nonpregnant than in pregnant women and, again, the question arises as to whether the greater percentage decreases in nonpregnant subjects depend upon the higher initial levels rather than upon a modified response in pregnancy. Exclusion of all subjects in either group whose control urine volumes were less than 6 ml/min gave comparable averages and ranges of control volumes in the two groups. In the seven nonpregnant women the mean decrease in urine flow was 84% in the first period and 90% in the second. In the six pregnant women\(^*\) the decreases were 51% and 57%, respectively. The mean decrease in urine volume was significantly less in pregnant than in nonpregnant women \((P < 0.01)\).

Angiotensin \(\text{II}\) was infused at the same rate of 0.5 \(\mu\)g/min in all patients; the dose per kg therefore varied from woman to woman. The average dose in the nonpregnant subjects was \(8.2 \times 10^{-3}\) \(\mu\)g/kg/min with a standard deviation of \(1.0 \times 10^{-3}\); in the pregnant women, the mean dose was \(7.8 \times 10^{-3}\) \(\mu\)g/kg/min \((\sigma = 1.56 \times 10^{-3})\). The difference is not significant \((t = 0.71, 0.5 > P >> 0.1)\). Khairallah et al.\(^24\) have studied the distribution of infused tritiated angiotensin \(\text{II}\) in female rats (no specification as to pregnancy) and found high concentrations of radioactivity in the adrenal, uterus, and kidney, in that order. It seems possible, then, that the greatly hypertrophied uterus of the pregnant woman might remove angiotensin from the circulation at a rapid rate, thus reducing the effective dose. However, the apparent effect of angiotensin upon the inulin clearance was as great in the pregnant women at term as in the nonpregnant (table 2).

The increased urinary tract dead space due to pyeloureteral dilatation during pregnancy poses a difficulty in measuring clearances and excretion rates accurately, especially when the urine volume output is low, variable, or de-
For this reason the first patients studied were subjected to ureteral catheterization, but this procedure proved unsatisfactory because of leakage around the ureteral catheters. Prolongation of the clearance periods seemed a good alternative to the stressful ureteral catheterization.

The effect to be expected from the dead space error when the urine volume falls would be apparent decreases in sodium excretion greater than the ones that actually occur. Therefore, the increased urinary tract dead space in pregnant women might be expected to give spurious data that would exaggerate the decreases. However, the apparent decreases in sodium excretion found in pregnant women were significantly less than those seen in nonpregnant subjects; the difference cannot be explained on the basis of dead space error because the change was in the wrong direction.

The spurious effect should be greater in the first clearance period than in the second. Reference to figures 1, 2, and 3 will show that the percentage decreases in apparent sodium excretion were usually quite similar in the two periods and that when there were differences, the greater change occurred in the second period as frequently as in the first.

The dead space error was small in most cases, as indicated by the following observations: (a) the depressions in excretion rates were similar in the first and second clearance periods, (b) rebounds in the inulin clearance—spurious or real—were seen in the post-infusion clearance periods in only one of five nonpregnant and one of nine pregnant women so studied, and (c) the inulin concentration in urine of the first period always increased unless the urine volume failed to fall, suggesting that dead space error in the second clearance period was at least partly overcome. There is some indication, however, from the serum inulin data that the apparent decreases in inulin clearance had been exaggerated by dead space error in the pregnant women. Presumably this would also mean that the apparent decreases in sodium excretion were greater than the ones that actually occurred.

The observations of the diminished pressor responses of pregnant women to angiotensin II confirm and extend the findings of Abdul-Karim and Assali. In the nonpregnant women the blood pressures at the end of the angiotensin II infusion averaged slightly less than the average maximal pressures. In 6 of the 10 cases, however, the maximal pressures were attained only at the end of the infusion. In contrast, the maximal blood pressures of the pregnant women usually were seen by the end of the first clearance period; thereafter, the pressures fell in 17 of the 20 women. In 4 of the 20 pregnant women the diastolic pressure returned to (or even fell below) control readings, and in 4 others the pressures near the end of the infusion were less than 5 mm Hg above the controls.

Although the angiotensin II infusions evoked smaller responses in blood pressure, urine volume output, and sodium excretion in pregnant than in nonpregnant women, the effect upon the inulin clearances of women near term may not have been different from that in nonpregnant women. This observation would cast some doubt upon the tempting assumption that the increased plasma levels of angiotensinase in pregnant women might explain their resistance to the other effects of angiotensin.

Women early in the third trimester of pregnancy showed depressions in their inulin clearances that averaged less than in the other two groups studied. Additional cases would perhaps show a statistically significant difference. As was noted above, angiotensin did not have the usual effect upon the PAH clearances in the three patients on whom this test was done.

Summary
Normotensive pregnant women are relatively resistant to angiotensin II in that they give smaller pressor responses and show smaller reductions in urine flow and sodium and chloride excretions than do normotensive nonpregnant women. Women early in the third trimester of pregnancy are more resistant to angiotensin II than are women at term, with respect to
the effect upon sodium and chloride excretions.

The less pronounced renal effects of angiotensin II in pregnant women cannot be attributed merely to error caused by increase in the dead space of the urinary tract.

References
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