Factors Controlling Plasma Renin and Aldosterone During Pregnancy

William H. Bay, M.D., and Thomas F. Ferris, M.D.

SUMMARY The response of plasma renin activity (PRA) and plasma aldosterone (PA) to change in sodium intake was evaluated in pregnant women during the third trimester. After 7 days on a 10 mEq sodium diet, PRA rose from 20.6 \( \pm \) 6.2 to 59.6 \( \pm \) 11.6 ng/ml/hr and PA from 47 \( \pm \) 11 to 127 \( \pm \) 27 ng% in pregnant women compared to PRA from 5 \( \pm \) 1.2 to 18.9 \( \pm \) 5.2 ng/ml/hr and PA from 7.7 \( \pm \) 1 to 42 \( \pm \) 3 ng% in nonpregnant controls. Pregnant women conserved sodium normally with urinary sodium excretion and weight loss similar to nonpregnant women. After 6 days on a 300 mEq sodium intake, PRA and PA in pregnant women were significantly higher, 10.2 \( \pm \) 1.4 ng/ml/hr and 22 \( \pm \) 3 ng%, respectively, compared to 1.5 \( \pm \) 0.3 ng/ml/hr and 7.3 \( \pm \) 1 ng% in controls. On both low- and high sodium intake there was a positive correlation between PRA and PA in pregnant women. Plasma prostaglandin E (PGE) was 0.45 \( \pm \) 0.06 ng/ml in pregnant women compared to 0.1 \( \pm \) 0.01 ng/ml in control women \((p < 0.01)\) and urinary PGE excretion was 2780 \( \pm \) 357 ng/24 hr in 28 pregnant women compared to 1191 \( \pm \) 142 ng/24 hr \((p < 0.01)\) in 14 nonpregnant controls. These findings indicate that although renin and aldosterone secretion respond to change in sodium intake in pregnancy, the cause of the increased renin secretion of pregnancy may be secondary to the increase that occurs in prostaglandin synthesis. (Hypertension 1: 410–415, 1979)

KEY WORDS renin • aldosterone • pregnancy • toxemia • prostaglandin E • sodium balance

PREGNANCY is associated with a striking increase in renin and aldosterone secretion. This has been attributed to either a salt-losing tendency induced by the increase in glomerular filtration rate (GFR) and progesterone secretion, orthostatic pooling in the extremities, or increased shunting of blood in the uterine circulation. However, blood volume, cardiac output, renal blood flow, and GFR all increase in pregnancy, which argues against functional volume depletion. In addition, the rise in renin secretion occurs in the first trimester before a great increase in uterine size or blood flow. Some studies have suggested no correlation between plasma renin activity (PRA) and plasma aldosterone (PA) in pregnancy, which suggests that factors other than sodium balance control renin secretion in pregnancy. To evaluate these questions, studies of PRA and PA were carried out in pregnant women in their third trimester on a low- and high-sodium intake. Since decreased sensitivity to angiotensin occurs during human pregnancy and renal prostaglandin synthesis may affect renin secretion, plasma and urinary PGE were also measured.

Methods

Normotensive women in their third trimester with no past history of renal or cardiovascular disease were admitted to the Clinical Research Center and placed on either a 10 or 300 mEq sodium 100 mEq potassium diet. Plasma renin and aldosterone were obtained before arising and at noon. Daily plasma electrolytes and 24-hour urine samples were obtained for creatinine clearance, urinary sodium and potassium determination. Nonpregnant hospital employees served as controls and were placed on the same diets, but were allowed to leave the metabolic unit during working hours. Plasma renin activity was measured by radioimmunoassay according to the method of Haber after incubation of plasma for 3 hours at pH 5.5.
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Weight change and urinary sodium excretion in pregnant and nonpregnant women on a 10 mEq sodium diet for 7 days.

Figure 1. Weight change and urinary sodium excretion in pregnant and nonpregnant women on a 10 mEq sodium diet for 7 days.

Figure 2. Plasma renin activity and aldosterone of pregnant and nonpregnant women on a 10 mEq sodium diet for 7 days.

Plasma and urinary aldosterone and prostaglandin E (PGE) were measured by radioimmunoassay methods previously reported from this laboratory. Recovery of tritiated PGE added to all urine and plasma samples reported in this paper was 73 ± 0.53% SEM. The values for plasma renin and aldosterone are those obtained at noon unless otherwise stated. Student's t tests were used for statistical evaluation of the results and all data are presented as the mean ± 1 SEM. Correlation coefficients were determined by a Hewlett-Packard Model 9830 Computer (Hewlett-Packard Co., Palo Alto, CA).

The protocol of this study was approved by the Human Experimentation Committee of the Ohio State University School of Medicine and informed and written consent was obtained from each patient.

Results

On the first day of the study, pregnant women had higher supine PRA, 12 ± 3 ng/ml/hr, than nonpregnant women, 2.4 ± 0.9 ng/ml/hr (p < 0.01). After being upright for 4 hours, PRA increased in pregnant women to 18 ± 3 compared to 4 ± 0.8 ng/ml/hr in control women. Plasma aldosterone increased with standing from 20 ± 3 to 36 ± 7 ng% in the pregnant women compared to from 6.3 ± 1 to 7.7 ± 0.8 ng% in controls.

On a daily 10 mEq sodium intake, pregnant and nonpregnant women came into sodium balance as shown in figure 1. By Day 4 pregnant and nonpregnant women had similar sodium excretion but over the next 7 days nonpregnant women had greater mean sodium loss (280 mEq) than pregnant women (215 mEq), although the difference was not statistically significant. Weight loss (1.5 kg) was similar over the 7-day period in both groups. Creatinine clearance was higher in pregnant women, 133 ± 4, compared to 117 ± 4 ml/min in nonpregnant women (p < 0.05) and no change occurred in either group during sodium restriction. On the low sodium diet pregnant and nonpregnant women had increased PRA and aldosterone levels (fig. 2); PRA rose in nonpregnant women from 5 ± 1.2 on Day 1 to 18.9 ± 5.2 ng/ml/hr (p < 0.01) on Day 7 and PA increased from 7.7 ± 1 to 42 ± 3 ng% (p < 0.01). In pregnant women, PRA rose from 20.6 ± 5 to 59.6 ± 11 ng/ml/hr (p < 0.01) and plasma aldosterone from 47 ± 11 to 127 ± 27 ng% (p < 0.01) on Day 7. Urinary aldosterone excretion in pregnant women rose from 66 ± 10 on Day 1 to 225 ± 37 μg/24 hrs (p < 0.01) on Day 7.

On the 300 mEq sodium intake, both groups were in sodium balance by Day 5. Pregnant women retained 170 mEq of sodium with a 1.2 kg weight gain. No weight gain occurred in controls as they came into sodium balance on the first day of the 300 mEq sodium intake. After 7 days of a 300 mEq sodium intake, serum potassium was unchanged in both groups. However, by Day 6, urinary sodium excretion was similar in both groups but PRA was 10.2 ± 1.4 ng/ml/hr and aldosterone 22 ± 3 ng% in pregnant women compared to 1.5 ± 0.3 ng/ml/hr and 7.3 ± 1 ng% in nonpregnant women. Figure 3 plots the supine PRA and PA in pregnant and nonpregnant women on the 300 mEq sodium intake.
Figure 4 demonstrates the correlation in pregnant women of mean PRA and PA over the 6 days of high sodium and 7 days of low sodium intake. The correlation coefficient was \( r = 0.95 \) on the low and \( r = 0.78 \) on the high sodium diet. The slope of the regression was similar in the pregnant and nonpregnant women on a low sodium intake. On the high sodium intake in the nonpregnant women, no significant change in PRA or PA occurred due to the initial high urinary sodium and low PRA and PA in these women on the first day of the study.

After 6 days of a 300 mEq sodium diet, two women from each group were given 2 liters of normal saline intravenously for 2 consecutive days during which time they remained recumbent. Despite bedrest and 4 liters of saline, the pregnant women had PRA of 3.5 ± 0.1 ng/ml/hr in nonpregnant women and their PA level was 12 ± 1 compared to 6 ± 2 ng%. Thus, upright posture is not necessary for persistence of renin secretion in pregnancy. The GFR was significantly higher in the pregnant women, 154 ± 12, compared to 115 ± 5 ml/min in nonpregnant women before the start of the high salt intake and in neither group did the GFR increase during sodium loading.

Figure 5 shows plasma prostaglandin E in 23 pregnant women in their third trimester and 19 nonpreg-
Discussion

Previous studies of pregnant women have consistently demonstrated an increase in renin and aldosterone secretion. However, there have been discrepant findings regarding their responsiveness to changes in sodium intake. Some studies have demonstrated a variation with changes in sodium intake. We found a significant correlation between PRA and PA on both a high and low sodium intake. Although on both high and low sodium intake PRA and PA were higher in pregnant women, the slope of the regression lines was similar for both pregnant and nonpregnant women on the low sodium diet (fig. 4).

The cause of the elevated PRA in pregnancy has been attributed to increased progesterone secretion, a known aldosterone antagonist. Progesterone secretion increases in the first trimester and parallels aldosterone secretion. When given to normal subjects or to patients with adrenal insufficiency on mineralocorticoid replacement, progesterone increases sodium excretion, and when applied to the isolated toad bladder it reduces sodium transport by displacing aldosterone from its binding site. In not all studies of pregnancy, however, has a correlation between plasma progesterone and plasma aldosterone been found. It is also difficult to explain the sodium retention, expansion of maternal extracellular volume, on the basis of antagonism to aldosterone and a tendency to natriuresis during pregnancy. Landau, and Lugibihl, failed to observe a natriuresis in pregnant women given progesterone, and women with Addison's disease do not require added mineralocorticoid replacement during pregnancy. Thus, mineralocorticoid antagonism does not appear to be a prominent feature of pregnancy, although the failure to develop hypokalemia with increased aldosterone secretion and normal sodium intake might be explained by the increased progesterone secretion. Hypokalemia associated with primary aldosteronism has been ameliorated during pregnancy.

The elevation of PRA, in spite of a high sodium intake, points to factors other than sodium that control renin secretion in pregnancy. Although compression of the inferior vena cava by the gravid uterus in late pregnancy might increase renin secretion, the elevated PRA prior to arising and after intravenous saline and

![Figure 5. Plasma prostaglandin E (PGE) in pregnant women in their third trimester and nonpregnant women.](http://hyper.ahajournals.org/)

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creatinin secretion is thought to represent renal synthesis since the
of PRA in third-trimester-pregnant women or that sodium intake and does not normally enter the mater-
experimental evidence in animals suggests that uterine
amniotic fluid contained mainly "big renin" since
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tration.
by feedback suppression of renin secre-
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renin concentration does not respond to change in
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of renin in pregnancy. Day et al.
17
' increases renin substrate concentration but this is not an
adequate explanation for the elevated PRA. No
significant increase in PRA usually occurs in women taking oral contraceptives containing estrogen,2, 17 probably due to feedback suppression of renin secre-
However, in pregnancy there is an increase in plasma renin, renin substrate, and angiotensin concen-

The uterus and amniotic fluid are potential sources
of renin in pregnancy. Day et al.18 found that human
amniotic fluid contained mainly "big renin" since
dialysis at pH 3.3 greatly increased renin activity. Experimental evidence in animals suggests that uterine renin concentration does not respond to change in sodium intake and does not normally enter the maternal circulation.18 The fact that PRA responded appropri-
ately to change in sodium intake in our studies makes it unlikely that uterine renin is a major source of PRA in third-trimester-pregnant women or that "big renin" activated by incubation at pH 5.5 contributes significantly to the hyper-reninemia of pregnancy.

The sources of the increased plasma and urinary PGE in pregnant women is unclear. Urinary PGE excretion is thought to represent renal synthesis since the
high prostaglandin dehydrogenase activity of renal cortex should oxidize circulating plasma PGE. Infu-
sions of PGE into the renal artery do not increase urinary PGE excretion.20 However, extraordinary
concentration of PGE have been found in the uterine vein of pregnant rabbits.8 Whether uterine PGE secre-
tion would increase plasma PGE concentration depends upon the extent to which PGE escapes metab-
olism during transit through the pulmonary circu-
lation. Studies in the cat and dog21 indicate that 90-95% of PGE is metabolized in one passage through the pulmonary capillary bed but in humans only 65% of PGE injected into the right ventricle is metabolized in the pulmonary circulation.22 Thus, an increase in uterine PGE synthesis could possibly elevate plasma PGE concentration.

The role of increased PGE synthesis in pregnancy is unknown. The uterus can synthesize prostaglandins of the E and F series and both may have a role in con-
trolling uterine motility.23 Prostaglandin-inhibiting
drugs reduce uteroplacental blood flow in the pregnant
rabbit2 although autoregulation of uterine blood flow is independent of prostaglandin synthesis. Uterine
synthesis of PGE might be necessary for new blood
vessel growth and development in the uterus and placenta during pregnancy. The vasodilation and in-
crease in blood volume induced by vasodilation would be a teleological advantage in pregnancy; protecting against hypotension and volume depletion if hemorrhage should accompany delivery.

Increase PGE synthesis may also be a factor in the
increase in renin secretion of pregnancy. Stimulation of renal prostaglandin synthesis by administration of arachidonic acid to rabbits and dogs increases renin secretion24 and indomethacin reduces renin se-
cretion.25 This effect appears to be independent of change in renal blood flow since prostaglandin syn-
thesis appears necessary for renin secretion during in
vitro studies of renal cortical cells.26

Synthesis of PGE may cause the insensitivity to angiotensin that occurs with pregnancy. Prostaglandin
antagonizes and inhibition of PGE synthesis enhances
the pressor effect of angiotensin and norepinephrine.
Angiotensin antagonism has been demonstrated in
human pregnancy as early as 10-12 weeks of gestation.27 Everett et al.28 have reported that indomethacin and aspirin reverse this insensitivity. Pregnancy could be similar to Bartter's syndrome where insensitivity to angiotensin, induced by PGE, is thought to cause compensatory increase in renin secre-
tion. Like pregnant women, patients with Bartter's syndrome have elevated PRA levels which vary with change in sodium intake and are not suppressed in response to volume expansion. Urinary PGE excre-
tion in Bartter's syndrome has been reported elevated to values similar to the results we found in pregnant women.29

One might speculate on the potential role of PGE synthesis in the development of hypertension with tox-
emia. Although PRA is variable in toxemia, angioten-
sin sensitivity increases and precedes the development

![Figure 6. Urinary prostaglandin E (PGE) excretion in pregnant (third trimester) and nonpregnant women.](http://hyper.ahajournals.org/)}
of hypertension. Conceivably, increased sensitivity to angiotensin with development of toxemia represents a decrease in PGE synthesis with resultant imbalance of the renin-angiotensin-PGE axis. Serial measurements of urinary PGE throughout pregnancy are needed to determine if changes in angiotensin sensitivity with toxemia can be correlated with urinary PGE excretion.

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References

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