Renal and Hormonal Effects of Water Deprivation in Late-Term Pregnant Rats

Sofía P. Salas, Andrea Giacaman, Carlos P. Vío

Abstract—Water-retaining hormones are stimulated during pregnancy allowing normal volume expansion. Because pregnant rats actively retain water, we postulate that water deprivation (WD) would cause a greater reduction in plasma volume in pregnant than in nonpregnant rats. To test this hypothesis, Sprague-Dawley pregnant and nonpregnant rats were water-deprived for 48 hours. At day 19 of pregnancy, or in the corresponding day in nonpregnant rats, they were randomly assigned to either a WD or a control (C) pair-fed group (n=10 to 12 per group). WD significantly reduced body weight, food intake, and creatinine clearance, and increased urinary osmolality in nonpregnant and pregnant rats. WD reduced plasma volume in a similar proportion in nonpregnant and pregnant rats (nonpregnant rats C=13.1±0.4, WD=11.0±0.2; pregnant rats C=19.4±0.7, WD=16.8±0.5 mL, P<0.001). Both groups of pregnant rats had a similar reduction in blood pressure. Plasma renin activity (nonpregnant rats C=6.1±1.1, WD=20.5±2.0; pregnant rats C=49±9.7, WD=94±12 ng angiotensin I/mL per hour, P<0.001) and plasma aldosterone levels were increased by pregnancy and further increased by WD. WD significantly reduced urinary kallikrein. WD caused a significant reduction in fetal but not placental weights. Present data indicate that 48-hour WD reduced renal kallikrein and further stimulated water-retaining hormones. We speculate that these are compensatory changes contributing to the maintenance of pregnancy in response to WD. (Hypertension. 2004;44:334-339.)

Key Words: preeclampsia ■ pregnancy ■ renin ■ bradykinin ■ aldosterone ■ kallikrein ■ mineralcorticoids

Normal pregnancy is characterized by several hemodynamic changes that allow a progressive increment in uteroplacental blood flow and adequate fetal growth. The initial event that triggers these hemodynamic changes is thought to be a drop in systemic resistance caused by an increase in vasodilator substances, such as NO and renal kallikrein. This systemic vasodilatation will stimulate the renin-angiotensin system (RAS) that, in turn, produces renal water and sodium retention.1–3 The increase in total body sodium is exceeded by the increase in total body water, causing a reduction in both plasma sodium and serum osmolality during normal gestation. Although in nonpregnant animals these changes would cause suppression of arginine vasopressin release and a water diuresis, volume-sensing mechanisms appear to adjust as pregnancy progresses, so that the new volume is sensed as normal.4 Thus, the central regulation of arginine vasopressin release maintains body tonicity at a lower steady-state value during pregnancy, and, furthermore, the threshold for thirst is reset to a lower plasma osmolality.5 Responses to sodium loading or to chronic mineralocorticoid administration indicate that pregnant and nonpregnant rats respond similarly. However, during salt restriction, gravid rats fail to expand their plasma volume normally, and this relative hypovolemia activates mechanisms leading to free water retention and pathological hyponatremia, responses not observed in nonpregnant animals.6

Water deprivation (WD) is a potent stimulus, which modifies the water and electrolyte balance, decreasing both extracellular and intracellular fluid volume. Consequently, we hypothesized the existence of quantitative differences in the hormonal and hemodynamic responses to WD between nonpregnant and pregnant rats. Specifically, we expected that because pregnant rats actively retain water, WD would cause a greater impact on plasma volume expansion in this group. The experiments reported here were performed to determine the influence of WD on plasma volume expansion, plasma renin activity (PRA), plasma aldosterone, and urinary kallikrein activity, as well as in renal function and reproductive outcome, in nonpregnant and in near-term pregnant rats.

Methods

Experimental Design

Female Sprague-Dawley rats, 230 to 250 g initial weight, were maintained at the Center for Medical Research animal care facilities in a controlled environment (22 to 24°C and a 12-hour light/dark cycle). All procedures met international guidelines for animal wel-
Rats were divided into 4 groups: nonpregnant control (n = 12), nonpregnant WD (n = 12), pregnant control (n = 10), and pregnant WD (n = 12). In the pregnant groups, rats in estrous phase were mated overnight with fertile males and the presence of sperm in the vaginal smear was considered as day 0. Nonpregnant rats were random-cycle littersmates. At day 19 of pregnancy, or at the equivalent time in nonpregnant rats, animals were individually placed in metabolic cages for 2 consecutive 24-hour periods. In the WD groups, access to water was completely suppressed for 48 hours (days 19 to 21), whereas free access was maintained to standard rat chow. Food intake in both groups of WD rats was recorded daily, and control animals were pair-fed according to daily average food intake of the corresponding WD group. Control groups had free access to water. An additional group of pregnant rats (n = 4) underwent 72-hour WD from days 18 to 21.

At day 21 of pregnancy, or in the corresponding day in nonpregnant rats, systolic blood pressure was measured by tail-cuff plethysmography. The rats were then anesthetized with xylazine (5 mg/kg) plus ketamine (40 mg/kg IP). Plasma volume was measured by the Evans blue dye dilution technique, and blood samples were obtained from the abdominal aorta, as described. An aliquot was used for microhematocrit determination, and the remainder was centrifuged and the plasma frozen for further determinations. Twenty-four-hour urine was measured, divided into aliquots, and stored frozen until analyzed. All determinations were performed at day 21 of pregnancy or in the corresponding day in nonpregnant rats, except for urine volume and food and water intakes, which were measured during days 19 to 20 and 20 to 21.

Net maternal body weight (after removal of all maternal organs including the uterus), litter size, and individual weights of fetuses and placentas were recorded. According to the 10th centile of birth weights obtained from all control fetuses, we estimated the percentage of fetuses whose birth weights were below the 10th centile in both WD groups.

Hormonal and Biochemical Measurements

PRA was determined by radioimmunoassay of generated angiotensin I under control conditions. Plasma aldosterone was measured by radioimmunoassay with the use of a commercial kit (Diagnostic Products Corporation). Urinary kallikrein activity was determined by the amidase method with the use of the synthetic substrate DL-Val-Leu-Arginine-β-nitroanilide (Sigma). Plasma and urinary electrolytes were measured with a Berkan autoanalyzer. Plasma and urinary creatinine levels were measured with a Beckman autoanalyzer. Urinary protein concentration was determined by the Bradford method (bio-rad protein assay). Serum and urinary osmolality were determined by freezing point (Advanced Instruments, model 3DII).

Statistical Analysis

Statistical analysis was performed using the computer program StatView II (Abacus Concepts Inc). All data were expressed as mean±SEM. Statistical significance was accepted at a level of P<0.05, and data were analyzed by a single-factor factorial design ANOVA or by a simple linear regression.

### Results

Maternal general characteristics are shown in Table 1. Main findings include a significant reduction in body weight in WD rats and a reduction in food intake after the second day of WD; this was more pronounced in pregnant than in nonpregnant rats. Systolic blood pressure was reduced by pregnancy and was unaffected by WD. Hematocrit values were lower in pregnant than in nonpregnant rats and were significantly increased by WD. Plasma volume levels were increased by pregnancy and reduced in both groups of WD rats. The highest plasma volume levels were observed in control pregnant rats (Table 1). Interestingly, percentage reduction in plasma volume after WD was similar in nonpregnant than in pregnant rats (16% versus 14%, nonsignificant). When all groups were combined, a significant negative correlation was observed between plasma volume and hematocrit levels (r = −0.9, P<0.001).

The main renal changes caused by WD are shown in Table 2. As expected, WD reduced urine output. Serum creatinine was similar in all groups (nonpregnant rats Control (C) = 0.4±0.03 versus WD = 0.4±0.03, pregnant rats C = 0.5±0.03 versus WD = 0.5±0.08 mg%). Urinary creatinine excretion was significantly reduced by WD (nonpregnant rats C = 8.3±0.9 versus WD = 5.0±0.5, P<0.001; pregnant rats C = 7.6±0.4 versus WD = 4.6±0.4 mg per day, P<0.001). In consequence, creatinine clearance was lower in both groups of WD rats. Serum osmolality was not affected.
by WD in nonpregnant rats and was significantly reduced in WD pregnant rats. Urinary osmolality was significantly increased by WD. WD decreased daily solute excretion in nonpregnant rats but did not change it in pregnant rats (nonpregnant rats C = 12.2 ± 1.0 versus WD = 6.5 ± 0.7, P < 0.001; pregnant rats C = 8.3 ± 0.9 versus WD = 6.5 ± 0.6; Osm per day). Urinary osmolality to serum osmolality ratio was increased in both groups of WD rats (nonpregnant rats C = 8.7 ± 1.7 versus WD = 18.7 ± 2.5, P < 0.001; pregnant rats C = 8.4 ± 1.1 versus WD = 20.9 ± 2.0, P < 0.001). WD significantly reduced urinary sodium excretion in nonpregnant rats but did not modify it in pregnant animals; both groups of pregnant rats had significantly lower sodium excretion than their corresponding nonpregnant groups. WD significantly reduced sodium fractional excretion in pregnant rats but not in nonpregnant rats. WD reduced osmolar clearance and free water reabsorption only in nonpregnant rats. (Table 2). When water reabsorption was expressed as a proportion of creatinine clearance, values were similar in all groups except for pregnant WD rats, which exhibited a greater value (data not shown).

As shown in the Figure, both groups of pregnant rats had significantly higher PRA levels than their corresponding nonpregnant groups. WD further increased PRA levels in pregnant rats, but the rise observed in nonpregnant rats was not statistically significant (6.1 ± 1.1 to 20.5 ± 2.0 ng angiotensin I (Ang I)/mL per hour). WD significantly increased aldosterone levels in both nonpregnant and pregnant rats; the highest values were observed in WD pregnant rats. Plasma aldosterone to PRA ratio was significantly reduced in pregnant rats when compared with the corresponding nonpregnant groups and was unaffected by WD (nonpregnant rats C = 88.4 ± 12 versus WD = 89.7 ± 18.3; pregnant rats C = 41 ± 7.9, WD = 38.2 ± 5.4, P < 0.01). When all groups were combined, a positive and significant correlation was observed between PRA and aldosterone levels (r = 0.68, P < 0.001). WD significantly reduced urinary kallikrein activity in nonpregnant and in pregnant rats (Figure). Urinary kallikrein activity had a positive correlation with creatinine excretion (r = 0.86, P < 0.001) and when urinary kallikrein activity was expressed per creatinine excretion, differences disappeared (data not shown).

Results of selected maternal and fetal variables obtained in rats that underwent 48-hour or 72-hour WD during late pregnancy are shown in Table 3. Maternal weight at term was significantly lower in 72-hour WD rats when compared with controls. Systolic blood pressure was unaffected by WD (not shown). WD did not modify litter size, and fetuses from all groups were alive when extracted from the uterus. WD decreased fetal weight, particularly in the 72-hour group, and increased the number of pups whose birth weights were below the 10th percentile (42/139 and 41/49 for 48-hour and 72-hour WD, respectively, χ² = 86, P < 0.001). Placental weight was unaffected by WD. Hematocrit (0.42 ± 0.006), plasma volume (16.6 ± 0.8 mL), serum creatinine (0.57 ± 0.2 mg%), creatinine clearance (0.8 ± 0.2 mL/min), PRA, and aldosterone levels were similar between 48-hour and 72-hour WD pregnant rats (Table 3). When compared with the 48-hour WD rats, serum osmolality was even lower (303 ± 5.5 mOsm/L, P < 0.05) and urinary osmolality was higher in the 72-hour WD group (8197 ± 1047 mOsm/L, P < 0.001); thus, urinary to serum osmolality ratio increased progressively with WD (Table 3).

**Discussion**

In the present study, we provide data showing quantitative differences between late pregnant and nonpregnant rats in

**TABLE 2. Renal Function in Nonpregnant and Pregnant Rats after 48-Hour Water Deprivation**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nonpregnant</th>
<th></th>
<th>Nonpregnant</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>48-Hour WD</td>
<td>Control</td>
<td>48-Hour WD</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(n=12)</td>
<td>(n=12)</td>
<td>(n=10)</td>
<td>(n=12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine volume day 19–20, mL</td>
<td>6.6 ± 0.8</td>
<td>4.0 ± 0.5</td>
<td>7.7 ± 1.1</td>
<td>5.3 ± 0.6</td>
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</tr>
<tr>
<td>Urine volume day 20–21, mL</td>
<td>5.3 ± 0.8</td>
<td>1.2 ± 0.2</td>
<td>3.5 ± 0.8†</td>
<td>1.1 ± 0.1*</td>
<td></td>
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</tr>
<tr>
<td>Creatinine Clearance, mL/min</td>
<td>1.5 ± 0.2</td>
<td>0.8 ± 0.1</td>
<td>1.1 ± 0.1†</td>
<td>0.7 ± 0.1*</td>
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<td></td>
</tr>
<tr>
<td>Serum osmolality, mOsm/L</td>
<td>348 ± 5.1</td>
<td>346 ± 7.5</td>
<td>339 ± 5.4</td>
<td>319 ± 6.0†</td>
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</tr>
<tr>
<td>Urinary osmolality, mOsm/L</td>
<td>2800 ± 424</td>
<td>6097 ± 503*</td>
<td>2866 ± 339</td>
<td>6316 ± 595*</td>
<td></td>
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</tr>
<tr>
<td>Plasma sodium, mEq/L</td>
<td>137 ± 0.7</td>
<td>140 ± 0.7</td>
<td>130 ± 1.0†</td>
<td>137 ± 1.0†</td>
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</tr>
<tr>
<td>Plasma potassium, mEq/L</td>
<td>3.8 ± 0.2</td>
<td>4.4 ± 0.1</td>
<td>3.8 ± 0.2</td>
<td>3.7 ± 0.2†</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Urinary sodium, mEq/d</td>
<td>0.59 ± 0.07</td>
<td>0.29 ± 0.02*</td>
<td>0.06 ± 0.02†</td>
<td>0.11 ± 0.02†</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Urinary potassium, mEq/d</td>
<td>1.13 ± 0.09</td>
<td>0.71 ± 0.09*</td>
<td>1.05 ± 0.1</td>
<td>0.84 ± 0.09</td>
<td></td>
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<tr>
<td>FE Na⁺</td>
<td>0.19 ± 0.02</td>
<td>0.18 ± 0.3</td>
<td>0.03 ± 0.02†</td>
<td>0.09 ± 0.01†</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>FE K⁺</td>
<td>14.3 ± 1.8</td>
<td>12.9 ± 1.4</td>
<td>17.3 ± 1.9</td>
<td>25.3 ± 5.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmolar clearance, μL/min</td>
<td>23 ± 2</td>
<td>11 ± 1*</td>
<td>17 ± 2†</td>
<td>14 ± 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free-water reabsorption, μL/min</td>
<td>19 ± 2</td>
<td>10 ± 1*</td>
<td>14 ± 2</td>
<td>13 ± 1</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Values are mean ± SEM.
†Differences between control and water-deprived groups.
* Differences between nonpregnant and pregnant rats, P < 0.05, ANOVA.
response to WD. Late-term pregnant rats were able to further stimulate renin and aldosterone above the already elevated values observed in normal pregnant rats. In addition, although the ability to concentrate urine in response to WD was similar in pregnant and nonpregnant rats, they exhibited differences in some parameters of renal function, such as a decrease in serum osmolality and changes in renal sodium excretion and in water reabsorption after WD.

Normal pregnancy, in humans and rats, is associated with important hormonal, biochemical, hemodynamic, and renal changes. In the pregnant rat, the increase in plasma volume occurs mainly during the last week of gestation, at the time this study was performed. Also, there is a marked increase in volume retaining hormones, such as renin and aldosterone, particularly near term. The renin-aldosterone system is a major determinant of sodium balance in pregnancy, opposing the natriuretic effects of several factors, such as filtered sodium, progesterone, and atrial natriuretic factor, among others. In the present study, 48-hour WD in late-term pregnant rats caused a marked increase in renin and aldosterone, above the already high values observed in normal pregnancy, indicating that this system is able to respond physiologically during pregnancy. Similar results have been reported in pregnant rats fed a low sodium diet, which was also able to stimulate renin and aldosterone. In the present study, when WD increased to 72 hours, PRA and aldosterone levels were not further elevated, indicating that the ability to secrete both hormones had reached a plateau. Aldosterone rise in response to WD is consistent with previous studies and is most likely secondary to stimulation of the renin-angiotensin system, as suggested by the positive and significant correlation observed between PRA and aldosterone levels. Additionally, increments on plasma concentration of angiotensin II and an increase in angiotensin II type-1 receptors in adrenal gland, which have been reported to occur during WD in nonpregnant rats, can contribute to the aldosterone rise.

WD caused a significant reduction in urinary kallikrein activity, both in nonpregnant and in pregnant rats. Similar results were reported in male rats. The mechanisms by which WD decreased urinary kallikrein activity were beyond the scope of the present study; however, we can speculate that it was secondary to the reduction in renal function, because differences disappeared when kallikrein values were expressed per creatinine excretion. This reduction may have

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=10)</th>
<th>48-Hour WD (n=12)</th>
<th>72-Hour WD (n=4)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight at term, g</td>
<td>335±6.7</td>
<td>320±5.4</td>
<td>302±9.8*</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>Litter size, n</td>
<td>11.2±0.4</td>
<td>11.6±0.4</td>
<td>12.0±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Fetal weight, g</td>
<td>5.0±0.05</td>
<td>4.7±0.05*</td>
<td>4.0±0.3†</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Placental weight, g</td>
<td>0.53±0.02</td>
<td>0.51±0.02</td>
<td>0.53±0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Fetal to placental ratio</td>
<td>9.5±0.4</td>
<td>9.3±0.2</td>
<td>7.5±0.1†</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>PRA, ng Ang I/mL per hour</td>
<td>49.0±9.7</td>
<td>94.2±12.1*</td>
<td>94.0±20*</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Aldosterone, nmol/L</td>
<td>3.96±0.6</td>
<td>8.91±0.8*</td>
<td>9.2±2.3†</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Urinary to serum osmolality ratio</td>
<td>8.4±1.1</td>
<td>20.9±2.0*</td>
<td>27±3.8†</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

* Differences between control and water-deprived groups.
† Differences between 48-hour WD and 72-hour WD, P<.05, ANOVA.
important functional consequences, because not only was kallikrein activity reduced, but a reduced density of B2-kinin-binding sites in the glomeruli of WD rats was also demonstrated. Thus, alterations in this vasoactive system may contribute to some of the renal functional alterations caused by WD. The kallikrein-kinin system is a vasoactive system that seems to participate in complex events such as regulation of blood pressure, control of the extracellular volume, sodium and water excretion, renal vascular resistance, and renin release. We have previously demonstrated that urinary kallikrein is increased in normal rat pregnancy. In the rat, the highest kallikrein levels are observed at midpregnancy, attaining prepregnancy values toward term. This time course can explain the fact that in the present study, late-term pregnant rats had kallikrein levels within the nonpregnant range. Interestingly, despite activation of the RAS and reduced kallikrein levels, water-deprived rats did not have higher blood pressure levels than controls and late-term pregnant rats exhibited the characteristic drop in blood pressure. A normal decrease in blood pressure, despite highly activated RAS, has also been reported in pregnant rats fed a low-sodium diet. Because the kallikrein-kinin system is likely to play an important role in counterbalancing the hemodynamic effects of the RAS, present results suggest the existence of other regulatory mechanisms involved in blood pressure regulation during pregnancy. Recently, it has been postulated that increases of different isoforms of nitric oxide synthase in the renal medulla of WD rats may have a role in the adaptation of renal function to volume depletion in the face of increments on systemic and intrarenal vasoconstrictor substances. However, it is unknown if similar changes are present in the systemic vasculature. In addition, there is evidence of an increased renal prostaglandin production, which may also counteract the action of systemic and intrarenal vasoconstrictor substances stimulated by WD.

WD caused a significant reduction in plasma volume and a rise in hematocrit, which is concordant with previous results. We had expected that because pregnant rats were actively retaining water, WD could cause a greater reduction on plasma volume in this group. However, the percentage decrease in plasma volume was almost identical to that observed in nonpregnant rats. This unexpected finding can be attributed to the observed differences in sodium excretion and percentage water reabsorption between nonpregnant and pregnant rats. Nonpregnant WD rats had a significant drop in daily sodium and potassium excretion that could reflect a reduction in the amount of filtrated sodium and potassium, because fractional excretion of both electrolytes was unchanged. When compared with nonpregnant rats, WD pregnant rats exhibited similar alterations in some parameters of renal function, such as a lower urine output and creatinine clearance, and concentrated urine. However, some important differences between nonpregnant and pregnant rats with respect to basal values and their responses to WD were observed. When compared with nonpregnant controls, pregnant rats had lower urine output and serum sodium, and nearly 10× lower daily sodium excretion; these changes are compatible with an active renal sodium and water retention. In fact, sodium fractional excretion was reduced in normal pregnant rats. Daily total solute excretion and osmolar clearance were also lower in pregnant rats. In contrast to what was observed in nonpregnant rats, WD pregnant rats did not further reduce sodium excretion or osmolar clearance, and water reabsorption remained unaltered. However, in proportion to filtration rate, pregnant WD rats reabsorbed more water. Another unexpected finding was that WD pregnant rats, although exhibiting reduced plasma volume and higher hematocrit values, had lower serum osmolality, which was further reduced after 72-hour WD. To what extent the previously mentioned differences between nonpregnant and pregnant rats could contribute to this finding, remains to be elucidated.

The lower birth weight observed in WD rats is compatible with the hemodynamic changes associated with WD. However, we cannot rule out the possibility of some direct nutritional effect caused by WD. Although control rats were pair-fed with WD, absolute maternal weight at term and net maternal weight were lower in WD rats. Moreover, pregnant rats seemed to be more affected by WD than nonpregnant animals, because food intake, particularly during the second day of WD, was lower than that of nonpregnant rats. A greater effect on birth weight was observed when WD was extended to 72 hours. Placental weight remained essentially unchanged, probably reflecting that at the moment when WD started, placenta had reached its maximum growth. Interestingly, plasma volume and hematocrit did not change further. However, kidneys were still able to produce more concentrated urine. Previous studies have shown that 3-day WD in late-term pregnant rats decreases plasma atrial natriuretic peptide concentration, which might contribute to the water-retaining mechanisms set in motion during WD.

Perspectives
In the present study, we demonstrated that 48-hour WD in late pregnant rats caused a significant reduction in volume expansion and in fetal weight. In addition, it further stimulated volume-retaining hormones, such as renin and aldosterone, above the already elevated values observed in normal pregnancy. However, after a 72-hour WD period, the RAS did not increase further, suggesting a plateau of the response. Nevertheless, kidneys were still able to produce more concentrated urine. It is of interest that the blood pressure—lowering effect of pregnancy, which is believed to be caused by systemic vasodilatation, was still present in water-deprived rats, despite their high renin and low kallikrein levels. Taken altogether, present data suggest that volume and hemodynamic regulation during pregnancy is a far more complex process in which many counterregulatory mechanisms can be involved to maintain adequate fetal survival.

Acknowledgments
This study was partially supported by grant 1.000.553 from Fondo Nacional de Ciencia y Tecnología (FONDECYT).

References
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Hypertension. 2004;44:334-339; originally published online July 26, 2004;
doi: 10.1161/01.HYP.0000138405.94275.a2

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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