The Conscious Instrumented Rabbit: A Model for the Study of Mechanisms of Blood Pressure Regulation During Pregnancy

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SUMMARY Conscious pregnant and nonpregnant rabbits were used to further evaluate the role of prostaglandin (PG) and plasma renin activity (PRA) in the systemic hemodynamics of pregnancy. Pregnant rabbits had high peripheral blood levels of both PGE₂ and PRA. Systemic blood pressure was not affected in either pregnant or nonpregnant by the administration of an inhibitor of prostaglandin synthesis. Pregnant rabbits, however, had a much larger decrease in blood pressure than nonpregnant animals when given the angiotensin I (AI)-converting-enzyme inhibitor, captopril. Pregnant rabbits were more resistant to the pressor effect of exogenous AI than nonpregnant animals. The pressor effect of AI increased in pregnant rabbits after the administration of meclofenamate and parturition but was not changed by volume expansion. In contrast, the sensitivity of nonpregnant rabbits to AI increased after volume expansion, but not after treatment with inhibitors of prostaglandin synthesis. These studies demonstrate that a remarkable similarity exists between pregnant rabbits and pregnant women in the pressor response to AI. This study is the first to correlate the vasopressor response to AI with PRA and the level of a circulating vasopressor prostaglandin in pregnant animals. The results strongly suggest that this model will be fruitful in further attempts to define the factors controlling systemic hemodynamics during pregnancy. (Hypertension 5: 514–520, 1983)

Key Words • Blood pressure • pregnancy • renin • PGE • conscious rabbits

Pregnant women are characteristically resistant to the pressor effects of exogenous angiotensin II (AI). This hemodynamic alteration of pregnancy is accompanied by changes in the circulating level of vasoactive hormones. The serum concentration of the potent vasoconstrictor AI, measured directly or as expressed by plasma renin activity (PRA), is increased in the latter half of pregnancy. The level of circulating prostaglandin E (PGE), a potent vasodilator, as well as other prostaglandins, are also elevated in mid to late pregnancy. The role of the renin-angiotensin system in the control of blood pressure responses during human pregnancy has not been fully defined. In contrast, based on their studies in women, Gant and associates have suggested that prostaglandins may mediate the resistance to exogenous vasopressor agents observed in pregnancy.

The changes in levels of vasoactive hormones that occur during the course of human pregnancy are mimicked by those observed in pregnant rabbits. In this species, increases in PRA and in peripheral PGE₂ concentration also occur during pregnancy. Data obtained from experiments in rabbits suggest that these hormones affect blood pressure control; in anesthetized pregnant rabbits, AI converting enzyme inhibitors decrease, while inhibitors of prostaglandin synthesis increase, systemic blood pressure.

Previous work exploring blood pressure control mechanisms during pregnancies in humans and animals suffers from various methodologic problems. The studies in women failed to correlate the changes in the resistance to exogenous vasopressor agents with the peripheral concentration of vasoactive hormones. Human studies also frequently failed to include control subjects. The studies in animals were generally performed under the conditions of acute surgery and/or anesthesia, conditions which themselves may alter hormone synthesis or release.
To further define the roles of prostaglandins and All in the control of blood pressure during pregnancy, we devised experiments to parallel as closely as possible the natural pregnant state. We, therefore, elected to study conscious, chronically instrumented, pregnant rabbits. The effect of meclofenamate, an inhibitor of prostaglandin synthesis, as well as captopril, an inhibitor of Al-converting enzyme on the mean arterial pressure (MAP) were assessed in these animals. The effect of meclofenamate, rapid volume expansion, and parturition on the sensitivity to exogenous All were also explored. These hemodynamic studies were correlated with changes in arterial levels of PGE₂ and PRA measured by radioimmunoassay. The results were compared with the observations made in nonpregnant control animals.

Methods

Pregnant and nonpregnant female New Zealand white rabbits weighing between 4 and 5 kg were studied. Standard laboratory chow and water were allowed ad libitum except during experiments or for 12 hours prior to instrumentation when both were withheld. Pregnant rabbits were instrumented between the 17th and 19th day and studied from the 21st through 28th day of gestation. Consequently, not all investigations could be performed in the same pregnant animals.

Instrumentation of the Rabbits

A surgical level of anesthesia was obtained with sodium pentobarbital administered intravenously. Surgery was performed using aseptic techniques. The left femoral artery and vein were isolated and ligated just distal to the inguinal ligament. Silastic catheters (OD 0.065 in. and ID 0.030 in.) were placed in both vessels. The catheters were advanced to the distal aorta and the inferior vena cava, respectively, and secured. The distal portions of the catheters were looped and secured with sutures. This allowed for movement of the animal's limb without kinking the catheters. The catheters were routed subcutaneously and brought out through a skin incision 1 inch below the point of the scapula. They were placed in the pockets of a fitted nylon mesh jacket, tied, and wrapped with gauze. The catheters were flushed daily with heparinized saline solution to maintain patency.

Animals were allowed to recovery fully as evidenced by normal appetite and motion. No animal was studied until at least 48 hours after surgery. The same rest interval was given after each experiment with the exception of the animals studied in the immediate post partum period.

Blood Pressure Determination

The rabbits were studied in a quiet room after they were allowed to become accustomed to a restraining cage. Arterial blood pressure was monitored with a Beckman pressure transducer (Beckman Instruments, Schiller Park, Illinois) on the arterial catheter. This reading was continuously recorded with a Beckman R411 Dynagraph. MAP was calculated by adding one third of the pulse pressure to the diastolic pressure.

Administration of Test Compounds

Meclofenamate (Parke-Davis, Morris Plains, New Jersey) 3 mg/kg body weight and captopril (SQ 14,225 Squibb and Sons) 3 mg/kg body weight were dissolved in 1 ml of 0.9% saline and administered through the venous catheter. A 0.9% saline solution (15 ml per kg body weight in 10 minutes) was infused intravenously using Harvard Pump Model 940, (Harvard Apparatus,Millis, Massachusetts).

Determination of Effective All Pressor Dose

An All (Hypertensin, Ciba, CIBA, Summit, New Jersey) solution of 6.25 μg/ml in 0.9% saline was infused via the venous catheter using the Harvard Pump. The effective pressor dose of All was defined as the amount of All required to reach a sustained increase in diastolic blood pressure of 20 mm Hg. After starting with a dose of 8 ng All kg⁻¹min⁻¹, increasing doses of 10.4, 16, 20.8, 32, 52, 80, 100 and 160 ng All kg⁻¹min⁻¹ were administered in steps of 3 minutes until the increase in diastolic blood pressure reached 20 mm Hg. If a 20 mm Hg rise was noted, the infusion was continued at that rate for 1 minute to ensure that the rise was sustained. The infusion was then discontinued. The animal was allowed to recover for a minimum of 10 minutes. Subsequently, a second All infusion was performed starting two doses below the first recorded effective pressor dose. The final effective pressor dose of All reported represents the mean of the two infusions. The All pressor dose after meclofenamate was determined beginning 30 minutes after the drug was administered. In contrast, only 10 minutes were allowed to elapse after rapid saline infusion was completed and the initiation of the All infusion used to determine the effective pressor dose. An average of more than 10 minutes of the stepped increase in All infusion rate was required to obtain a 20 mm Hg rise in diastolic pressure. Therefore, the first effective pressor dose was determined about 20 minutes and the second about 40 minutes after the start of the saline infusion.

Nonpregnant rabbits appeared to be strikingly insensitive to exogenously administered All. Consequently, an All dose response curve was established in another six pregnant (21st to 28th day of gestation) and six nonpregnant animals by infusing 22, 44, 85, and 170 ng angiotensin II kg⁻¹min⁻¹ for sequential periods of 5 minutes each.

Blood Sampling

Blood sampling experiments were considered separate studies and not performed on the same day as the hemodynamic studies in any rabbit. This precaution was taken to avoid possible effects of volume changes on All sensitivity or blood pressure. Blood was collected before and beginning at 30 minutes after the administration of meclofenamate, captopril, or saline. The blood sampling experiments took place in a quiet
room and were performed in animals who had not had either surgery or been subject to another experimental protocol for at least 48 hours. In pregnant rabbits, this also implied that blood was collected only between the 21st through the 28th day of gestation. Blood sampling for a particular portion of the study (i.e., captopril, meclofenamate, or saline) was usually but not always performed in the same rabbits who had been subjected to hemodynamic studies with that compound. The samples used to assess the effect of parturition on PGE and PRA were collected in the period between 1 to 4 days prior to delivery and repeated 2 days after delivery.

Arterial blood for PGE determination was collected in tubes to which 50–70 ng indomethacin was added. Arterial blood for PRA determination was collected in tubes containing EDTA. Blood was kept at 4°C and centrifuged in the cold. The serum or plasma was kept frozen at minus 20°C until the time of assay.

Radioimmunoassay

The PRA was measured using a commercially available kit (Clinical Assays, Cambridge, Massachusetts). The radioimmunoassay for PGE, was originally described in 1975 by Venuto et al. This technique has been slightly modified, in that we now employ a highly specific antiserum against PGE, prepared in rabbits by Dr. F. Dray and B. Charbonnel at the Institut Pasteur, Paris, France. To avoid the potential problem of interassay variation, samples from an individual experiment were always analyzed in a single assay.

Determination of 24-Hour Sodium Excretion

Three pregnant rabbits were placed in metabolic cages to enable collection of urine beginning 3 days prior to delivery and ending with the 4th day post partum. Twenty-four-hour urinary sodium excretion was determined using a sodium-potassium analyzer (Nova I, Nova Biomedical, Newton, Massachusetts).

Statistics

Data are presented as the means ± the standard error of the mean (se). The Student’s ‘’t’’ test for paired data was employed to analyze the two phase experiments. Otherwise the Student’s ‘’t’’ test for unpaired data or the Mann-Whitney Wilcoxon test was used.

Results

The MAP in pregnant rabbits between Days 21 and 28 of gestation was 77 ± 3.5 mm Hg (37 determinations in 17 rabbits) and 81 ± 2.6 mm Hg in nonpregnant rabbits (42 determinations in 15 rabbits). The PRA in pregnant rabbits (n = 22) was higher than in nonpregnant controls: 11.1 ± 1.7 ng angiotensin I ml⁻¹hr⁻¹ compared to 5.9 ± 1.5 ng angiotensin I ml⁻¹hr⁻¹ (n = 21; p < 0.05). Arterial PGE, was also higher in pregnant rabbits: 1820 ± 213 pg/ml (n = 32) vs 157 ± 21 pg/ml in nonpregnant animals (n = 34; p < 0.001). Although slightly more exogenous All was required to increase diastolic blood pressure by 20 mm Hg in pregnant rabbits (21 studies in 17 animals), this response to the ‘‘effective pressor dose’’ of All was not significant (63 ± 5 ng All kg⁻¹min⁻¹ vs 55 ± 5 ng All kg⁻¹min⁻¹ respectively). However, the All dose-response curves revealed significant differences between pregnant and nonpregnant rabbits at doses of 44, 85, and 170 ng All kg⁻¹min⁻¹ (fig. 1).

Intravenous meclofenamate (3 mg/kg) failed to influence MAP in either pregnant or nonpregnant rabbits (from 79 ± 6 to 77 ± 5 mm Hg, n = 9, vs from 81 ± 5 to 79 ± 5 mm Hg; n = 8 respectively). At 30 minutes after the injection, however, a fall in PRA was measured in pregnant animals while no change was observed in nonpregnant rabbits (table 1). Consequently, the difference in PRA between pregnant and nonpregnant rabbits presented prior to treatment disappeared. Meflofenamate injected intravenously also decreased arterial PGE, concentration in pregnant rabbits; the decrease in arterial PGE, in nonpregnant rabbits failed to reach levels of statistical significance (table 2). Despite the fall in arterial PGE, of more than 60% observed in pregnant rabbits following meclofenamate, the concentration of this hormone was still higher than the level in nonpregnant animals prior to treatment with this inhibitor of prostaglandin synthesis (p < 0.01). Finally, after intravenous meclofenamate, the All responsiveness in pregnant animals increased while ‘‘no change’’ was noted in the nonpregnant rabbits (fig. 2).

Captopril (3 mg/kg) lowered mean arterial blood pressure in both pregnant (n = 7) and nonpregnant rabbits (n = 8) (from 73 ± 4 to 59 ± 4 mm Hg and from 74 ± 3 to 70 ± 2 mm Hg respectively). The more pronounced fall in MAP after captopril in pregnant animals was significantly different (p < 0.01) from that observed in the nonpregnant controls. Intra-
TABLE 1. Plasma Renin Activity (PRA) Before and 30 Minutes after Intravenous Meclofenamate, Captopril, and Saline Treatment in Pregnant and Nonpregnant Rabbits

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pregnant</th>
<th>Nonpregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre (ng AI ml⁻¹ hr⁻¹)</td>
<td>Post (ng AI ml⁻¹ hr⁻¹)</td>
</tr>
<tr>
<td>Meclofenamate</td>
<td>(n = 12) 10.9 ± 2.6</td>
<td>7.2 ± 1.8†</td>
</tr>
<tr>
<td>Captopril</td>
<td>(n = 4) 15.6 ± 4.1</td>
<td>55 ± 6.7†</td>
</tr>
<tr>
<td>Saline</td>
<td>(n = 6) 8.4 ± 2.1</td>
<td>3.6 ± 0.6†</td>
</tr>
</tbody>
</table>

Pre refers to arterial PRA concentration before, and Post designates PRA concentration 30 minutes after, the treatment. Statistical comparisons were made between rabbits in the same group before and after treatment. †p < 0.05; ‡p < 0.01; §p < 0.025.

TABLE 2. Arterial Prostaglandin E₂ (PGE₂) Concentration Before and 30 Minutes after Intravenous Meclofenamate, Captopril, and Saline Treatment in Pregnant and Nonpregnant Rabbits

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pregnant</th>
<th>Nonpregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre (pg/ml)</td>
<td>Post (pg/ml)</td>
</tr>
<tr>
<td>Meclofenamate</td>
<td>(n = 14) 2006 ± 713</td>
<td>730 ± 200†</td>
</tr>
<tr>
<td>Captopril</td>
<td>(n = 11) 1441 ± 203</td>
<td>1439 ± 279</td>
</tr>
<tr>
<td>Saline</td>
<td>(n = 7) 2248 ± 749</td>
<td>1623 ± 843</td>
</tr>
</tbody>
</table>

Pre refers to arterial PGE₂ concentration before and Post designates PGE₂ concentration 30 minutes after, the treatment. Statistical comparisons were made between rabbits in the same group before and after treatment. *p < 0.10; †p < 0.05.

Venous captopril increased PRA in both pregnant and nonpregnant rabbits (table 1). Following captopril, the arterial PGE₂ concentration was unchanged in pregnant rabbits but higher in nonpregnant animals (table 2). It is noteworthy that the majority of pregnant animals delivered or aborted within 24 hours after the administration of captopril.

Rapid infusion of 0.9% NaCl (15 ml/kg over 10 minutes) did not alter MAP in either group of rabbits (from 80 ± 5 to 76 ± 4 mm Hg in pregnant, n = 8, and from 90 ± 7 to 91 ± 8 mm Hg in nonpregnant, n = 7, animals). PRA, however, decreased following saline in all animals (table 1). The arterial PGE₂ level did not change significantly in the pregnant or nonpregnant rabbits following the infusion (table 2). Rapid volume expansion increased vascular sensitivity to exogenous All in nonpregnant rabbits but failed to alter the resistance to All in pregnant rabbits (fig. 3).

Following parturition, the sensitivity to exogenous All increased for the first 2 days (fig. 4). Ultimately, the animals required as much exogenous All to increase diastolic blood pressure by 20 mm Hg as was needed in nonpregnant animals. Table 3 depicts the arterial PGE₂ and PRA values obtained in 6 rabbits prior to and 2 days after delivery. The level of these hormones decreased precipitously following parturition. The sequential changes in 24-hour sodium excretion studied prior to delivery and daily thereafter are shown in table 4. In all three rabbits, sodium excretion had increased dramatically by the third day after delivery.
FIGURE 3. The amount of angiotensin II (AII) required to raise diastolic blood pressure by 20 mm Hg prior to (Pre) and 30 minutes after (Post) rapid saline infusion is shown on a logarithmic scale. Twelve studies were obtained in seven nonpregnant rabbits and 12 studies were obtained in eight pregnant rabbits. Dots connected by dashed lines depict mean values for each group.

FIGURE 4. The amount of angiotensin II (AII) required to raise diastolic blood pressure by 20 mm Hg before and after delivery is depicted on a logarithmic scale. The number of rabbits studied at each point is listed. The individual points are mean values bracketed by the standard error of the mean.

TABLE 3. Arterial Prostaglandin E2 (PGE2) Concentration and Plasma Renin Activity (PRA) in Six Rabbits Before and 2 Days After Delivery

<table>
<thead>
<tr>
<th>PGE2 (pg/ml)</th>
<th>PRA (ng AII ml⁻¹ hr⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior</td>
<td>Post</td>
</tr>
<tr>
<td>2651 ± 499</td>
<td>617 ± 75*</td>
</tr>
<tr>
<td>6.3 ± 1</td>
<td>2.9 ± 0.6*</td>
</tr>
</tbody>
</table>

*p < 0.01.

TABLE 4. Daily Sodium Excretion (mEq/24 hr) in Three Rabbits from Late Pregnancy Through the Fourth Day Post Partum

<table>
<thead>
<tr>
<th>Rabbit</th>
<th>Before Day of Delivery</th>
<th>Postpartum Day</th>
<th>2 Days</th>
<th>1 Day</th>
<th>1 Day</th>
<th>2 Days</th>
<th>3 Day</th>
<th>4 Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6.5 9.7 5.0 5.5 21.5 12.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>8.1 8.6 5.7 2.0 7.6 24.8 16.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>7.9 7.2 5.0 2.9 23.3 19.3 12.5</td>
<td></td>
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Discussion

The resistance to the pressor effect of exogenous AII that develops during pregnancy is an unexplained phenomenon. The demonstration of increased peripheral blood levels of potent vasoactive hormones like PGE2 and AII in gravid animals and women has fueled speculation that these substances may have a major role in the control of systemic blood pressure and the response to vasopressor stimuli during gestation. This study sought to further explore the relationship between these hormones and the blood pressure control during pregnancy. The experiments employed rabbits, a species characterized by changes in PRA and PGE during pregnancy that are similar in direction to those observed in pregnant women.

The animal model used in our experiments was free of the acute effects of anesthesia or surgery, a major difference from many previous studies. In such studies, systemic blood pressure of pregnant animals rose after the administration of inhibitors of prostaglandin synthesis. In contrast, when the conscious pregnant rabbits employed in the current experiments were treated with a dose of meclofenamate sufficient to reduce arterial PGE2 by 60%, no change in arterial blood pressure was observed. In anesthetized pregnant animals, the release of renin and other vasopressor compounds may comprise the response to the effects of anesthesia and surgery, as well as to the increased levels of circulating prostaglandin that characterizes the gravid state. One can speculate that removal of the vascular effects of PGE2 or other vasodilatory prostaglandins may result in unopposed vasoconstriction and increased blood pressure when acutely prepared pregnant animals are treated with an inhibitor of prostaglandin synthesis. Our findings in conscious pregnant rabbits suggest that circulating prostaglandins either have little role in the minute-to-minute regulation of systemic blood pressure during pregnancy or that the vasodilatory effect of PGE2 or other prostaglandins with similar vasoactive properties is carefully balanced by changes in All or other vasoconstrictors. Since the administration of meclofenamate to the preg-
nant rabbits resulted in a concomitant reduction in renin as well as PGE₂, our studies cannot further define this issue.

The studies with captopril support the concept that endogenous All plays an important role in maintaining systemic blood pressure during pregnancy. Administration of captopril to pregnant rabbits resulted in a blood pressure reduction three times greater than that observed in the nonpregnant controls. The contrast between the hormonal response in the pregnant and nonpregnant animals is also notable. In the pregnant animals, arterial PGE₂ did not change after captopril was given, while in nonpregnant animals the mean arterial PGE₂ rose. In this regard, our results in nonpregnant rabbits are similar to those of Swartz et al. who found that the level of metabolites of PGE₂ was increased in the peripheral blood of nonhypertensive human subjects receiving captopril. The observation of frequent spontaneous abortions following the administration of captopril to pregnant rabbits confirms the preliminary report of Jahneke et al.

Nonpregnant rabbits studied prior to meclofenamate or saline administration exhibited a striking resistance to the pressor effect of exogenous All. Although the “effective pressor dose” of All required in the nonpregnant animals was lower than needed in pregnant animals, the difference was not significant. The All dose response curves, however, revealed a distinct difference in All sensitivity between pregnant and nonpregnant rabbits at higher doses of exogenously administered All. These results are comparable to that reported by Berssenbrugge et al. Sensitivity to All was enhanced in pregnant but not in nonpregnant rabbits following treatment with meclofenamate. The change in resistance to All may have been a consequence of the precipitous decline in arterial PGE₂ concentration observed in the pregnant rabbits. Meclofenamate, however, also reduced PRA in the pregnant animals. Resistance to the pressor effect of exogenous angiotensin is characterized related to endogenous angiotensin II levels. It might be argued that the fall in PRA and presumably endogenous All, could explain the heightened response to exogenous All observed in pregnant rabbits following meclofenamate. Yet the results of the saline infusion studies make this explanation unlikely. Following rapid infusion of saline, PRA levels fell in both groups of rabbits. The sensitivity to exogenous All, however, increased only in the nonpregnant rabbits.

The two groups of experiments collectively suggest that the large quantity of PGE₂, or other vasodilatory prostaglandins present in the peripheral circulation of pregnant rabbits may mediate resistance to the pressor effect of All. Although PRA is also high, endogenous All does not seem to play a major role in the decreased sensitivity to exogenous All in pregnant rabbits.

The diminished sensitivity to All exhibited by pregnant rabbits is comparable to the findings in pregnant women. Resistance to the pressor effect of All is decreased in pregnant women following treatment with inhibitors of prostaglandin synthesis but not after volume expansion. It had been hypothesized that locally produced and acting vasodilator prostaglandins might be the cause of the increased resistance. The apparent inverse correlation, however, of the resistance to All with the circulating PGE₂ concentration of presumed uteroplacental origin, is impressive and suggests that the phenomena are related, at least in this model. We cannot exclude the possibility that other products of the arachidonic acid-cyclooxygenase pathway also are important in regulating the response to All in this or other species during pregnancy. It has, for example, been suggested that prostacyclin might be the primary circulating vasodepressor prostaglandin in dogs.

Termination of pregnancy dramatically altered the sensitivity to exogenous All. The group of rabbits studied with almost daily All infusion tests were uniformly very resistant to the pressor effect of this compound prior to delivery. A decrease in the amount of All required to raise diastolic BP by 20 mm Hg was observed following parturition; this trend reached its nadir at approximately 48 hours. A return to a level of sensitivity to All that typified nonpregnant rabbits developed over the ensuing 48 to 72 hours. The additional tests that were performed in other rabbits during this period may help to explain these observations. From late pregnancy to 48 hours post partum both arterial PGE₂ and PRA fell dramatically. The temporal relationship between the reduction in resistance to exogenous All and the decrease in circulating PGE₂ further supports a role for prostaglandins in mediating the altered sensitivity to All during pregnancy. The markedly increased sensitivity to exogenous All recorded 2 days post partum may relate to persistent sodium retention that is accumulated throughout pregnancy and mobilized in the postpartum period. In defense of this hypothesis is the correlation of an apparent natriuresis that developed in the first few days post partum with the return toward a level of resistance to All that typifies nonpregnant rabbits. Since sodium intake was not controlled, this explanation must remain as a conjecture.

In conclusion, these studies strongly suggest that vasodilator prostaglandins like PGE₂, are crucial in mediating the resistance to the pressor effect of exogenous All that develops during pregnancy in rabbits. Furthermore, conscious, instrumented pregnant rabbits exhibit a pattern of response to exogenous All similar to those previously described in pregnant women. It therefore appears that this animal preparation offers a model for further study of the physiology of blood pressure control mechanisms during pregnancy.

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