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 devise experiments to parallel as closely as possible the natural pregnant state. We, therefore, elected to devise experiments to parallel as closely as possible the natural pregnant state. We, therefore, elected to devise experiments to parallel as closely as possible the natural pregnant state. We, therefore, elected to devise experiments to parallel as closely as possible the natural pregnant state. We, therefore, elected to devise experiments to parallel as closely as possible the natural pregnant state. We, therefore, elected to devise experiments to parallel as closely as possible the natural pregnant state. We, therefore, elected to devise experiments to parallel as closely as possible the natural pregnant state. 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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 PGE₂ and PRA were collected in the period between 1 to 4 days prior to delivery and repeated 2 days after delivery.

Arterial blood for PGE₂ 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 PGE₂, originally described in 1975 by Venuto et al. The technique has been slightly modified, in that we now employ a highly specific antiserum against PGE₂, 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 (SEM). 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⁻¹·hr⁻¹ compared to 5.9 ± 1.5 ng angiotensin I ml⁻¹·hr⁻¹ (n = 21; p < 0.05). Arterial PGE₂ 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⁻¹·min⁻¹ vs 55 ± 5 ng All kg⁻¹·min⁻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⁻¹·min⁻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. Meclofenamate injected intravenously also decreased arterial PGE₂ concentration in pregnant rabbits; the decrease in arterial PGE₂ in nonpregnant rabbits failed to reach levels of statistical significance (table 2). Despite the fall in arterial PGE₂ 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-
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.
Pre-pregnant Pregnant

![Graph showing changes in blood pressure and angiotensin II levels before and after delivery.](image)

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

| Rabbit | Before 2 Days Before 1 Day Before Delivery Day 1 Day 2 Day 3 Day 4 |
|--------|------------------|--------------------|-----------------|-----------------|-----------------|
| A      | 6.5              | 9.7                | 2.4             | 5.0             | 5.5             | 21.5            | 12.7            |
| B      | 8.1              | 8.6                | 5.7             | 2.0             | 7.6             | 24.8            | 16.0            |
| C      | 7.9              | 7.2                | 5.0             | 2.9             | 23.3            | 19.3            | 12.5            |

**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 AII or other vasoconstrictors. Since the administration of meclofenamate to the preg-
nant rabbits resulted in a concomitant reduction in renin as well as PGE\textsubscript{2}, our studies cannot further define this issue.

The studies with captopril support the concept that endogenous AII 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 PGE\textsubscript{2} did not change after captopril was given, while in nonpregnant animals the mean arterial PGE\textsubscript{2} rose. In this regard, our results in nonpregnant rabbits are similar to those of Swartz et al,\textsuperscript{21} who found that the level of metabolites of PGE\textsubscript{2} 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 Jahnke et al.\textsuperscript{11}

Nonpregnant rabbits studied prior to meclofenamate or saline administration exhibited a striking resistance to the pressor effect of exogenous AII. Although the "effective pressor dose" of AII required in the nonpregnant animals was lower than needed in pregnant animals, the difference was not significant. The AII dose response curves, however, revealed a distinct difference in AII sensitivity between pregnant and nonpregnant rabbits at higher doses of exogenously administered AII. These results are comparable to that reported by Berssenbrugge et al.\textsuperscript{22}

Sensitivity to AII was enhanced in pregnant but not in nonpregnant rabbits following treatment with meclofenamate. The change in resistance to AII may have been a consequence of the precipitous decline in arterial PGE\textsubscript{2} concentration observed in the pregnant rabbits. Meclofenamate, however, also reduced PRA in the pregnant animals. Resistance to the pressor effect of exogenous angiotensin is characteristically related to endogenous angiotensin II levels. It might be argued that the fall in PRA and presumably endogenous AII, could explain the heightened response to exogenous AII 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 AII, however, increased only in the nonpregnant rabbits.

The two groups of experiments collectively suggest that the large quantity of PGE\textsubscript{2} or other vasodilatory prostaglandins present in the peripheral circulation of pregnant rabbits may mediate resistance to the pressor effect of AII. Although PRA is also high, endogenous AII does not seem to play a major role in the decreased sensitivity to exogenous AII in pregnant rabbits.

The diminished sensitivity to AII exhibited by pregnant rabbits is comparable to the findings in pregnant women. Resistance to the pressor effect of AII is decreased in pregnant women following treatment with inhibitors of prostaglandin synthesis but not after volume expansion.\textsuperscript{6, 14} It had been hypothesized that locally produced and acting vasodilator prostaglandins might be the cause of the increased resistance.\textsuperscript{8} The apparent inverse correlation, however, of the resistance to AII with the circulating PGE\textsubscript{2} concentration of presumed uteroplacental origin,\textsuperscript{13} 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 AII in this or other species during pregnancy. It has, for example, been suggested that prostacyclin might be the primary circulating vasodepressor prostaglandin in dogs.\textsuperscript{23}

Termination of pregnancy dramatically altered the sensitivity to exogenous AII. The group of rabbits studied with almost daily AII infusion tests were uniformly very resistant to the pressor effect of this compound prior to delivery. A decrease in the amount of AII 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 AII 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 PGE\textsubscript{2} and PRA fell dramatically. The temporal relationship between the reduction in resistance to exogenous AII and the decrease in circulating PGE\textsubscript{2} further supports a role for prostaglandins in mediating the altered sensitivity to AII during pregnancy. The markedly increased sensitivity to exogenous AII 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 AII 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 PGE\textsubscript{2}, are crucial in mediating the resistance to the pressor effect of exogenous AII that develops during pregnancy in rabbits. Furthermore, conscious, instrumented pregnant rabbits exhibit a pattern of response to exogenous AII 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.

Acknowledgments

The authors acknowledge the expert technical assistance of Peter Barone, Cathy Hubbard, Darlene Hart, and the secretarial assistance of Sandra Anzalone. The authors are also grateful for the critical review of the manuscript by Dr. Martin E. Plaut.
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Hypertension. 1983;5:514-520
doi: 10.1161/01.HYP.5.4.514

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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