Angiotensin II indirectly vasoconstricts the ovine uterine circulation

BLAIR E. COX, CARRIE E. WILLIAMS, AND CHARLES R. ROSENFIELD
Department of Pediatrics, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas 75235

Cox, Blair E., Carrie E. Williams, and Charles R. Rosenfeld. Angiotensin II indirectly vasoconstricts the ovine uterine circulation. Am. J. Physiol. Regulatory Integrative Comp. Physiol. 278: R337–R344, 2000.—The uterine vasculature of women and sheep predominantly expresses type 2 ANG II receptors that do not mediate vasoconstriction. Although systemic ANG II infusions increase uterine vascular resistance (UVR), this could reflect indirect mechanisms. Thus we compared systemic and local intra-arterial ANG II infusions in six near-term pregnant and five ovariectomized nonpregnant ewes to determine how ANG II increases UVR. Systemic ANG II dose-dependently (P > 0.001) increased arterial pressure (MAP) and UVR and decreased uterine blood flow (UBF) in pregnant and nonpregnant ewes; however, nonpregnant responses exceeded pregnant (P < 0.001). In contrast, local ANG II infusions at rates designed to achieve concentrations in the uterine circulation comparable to those seen during systemic infusions did not significantly decrease UBF in either group, and changes in MAP and UVR were absent or markedly attenuated. When MAP rose during local ANG II, which only occurred with doses ≥2 ng/ml, increases in MAP were delayed more than twofold compared with responses during systemic ANG II infusions and always preceded decreases in UBF, resembling that observed during systemic ANG II infusions. These observations demonstrate attenuated uterine vascular responses to systemic ANG II during pregnancy and suggest that systemic ANG II may increase UVR through release of another potent vasoconstrictor(s) into the systemic circulation.

PREGNANCY IS CHARACTERIZED by establishment of the uteroplacental circulation and a >30-fold rise in uterine blood flow (UBF) by term (34). The latter insures that oxygen and nutrient delivery to the rapidly growing fetus remains adequate throughout gestation (34). The mechanisms responsible for the increase in uteroplacental perfusion and its maintenance are not understood. In women and sheep, circulating levels of ANG II rise greater than fourfold during pregnancy (22, 23), and systemic ANG II infusions dose-dependently increase uterine vascular resistance (UVR) and arterial pressure (7, 8, 17, 18, 30, 37, 43). However, pressor responses are attenuated in pregnancy (19, 34, 37), and uteroplacental vascular responses are substantially less than simultaneous pressor responses (17, 30, 40). This difference in uteroplacental and systemic responsiveness may reflect mechanisms that protect the uterine vascular bed from the effects of normally increased plasma levels of ANG II during pregnancy. This is supported by reports that uteroplacental refractoriness to ANG II is absent in women with pregnancy-induced hypertension (18), which may add to the fetal mortality and morbidity associated with these pregnancies (12, 13). Therefore, it is important to understand how ANG II mediates its effects on the uteroplacental vascular bed and what accounts for the attenuated uterine vascular responsiveness normally seen in pregnancy.

Several mechanisms may contribute to the attenuated uteroplacental vasoconstrictor responses. Although plasma ANG II levels are elevated in normotensive pregnant women (23) and sheep (22), uterine artery smooth muscle ANG II-receptor (ATR) binding density is not downregulated and binding affinity is unchanged (10, 11, 22, 35). Thus neither appears to modify uteroplacental or systemic vascular responses to infused ANG II. There is evidence, however, that basal synthesis of endothelium-derived prostacyclin and nitric oxide (NO) increase during pregnancy and that ANG II further augments their synthesis by uterine arteries (24, 26, 28). Thus increases in adjacent vascular smooth muscle contents of cAMP and cGMP, respectively, may attenuate uterine vascular responses to ANG II and other agonists. Alternatively, this refractoriness may reflect the ATR subtype expressed in uterine artery smooth muscle. The AT₁R is expressed in most adult tissues and mediates virtually all known biological actions of ANG II, including calcium-mediated smooth contraction (2, 9, 10). The AT₁R is the product of a separate gene located on the x chromosome and has about 40% amino acid sequence homology with the AT₂R (21). The AT₂R has not been shown to mediate smooth muscle contractions (2, 9, 15), and although it remains unclear if it is capable of mediating vasodilation, coexpression with the AT₁R has been associated with attenuated smooth muscle contraction responses (9). The mechanism for this antagonism is presently unclear. In uterine vascular smooth muscle from nonpregnant and pregnant women and sheep, the AT₂R accounts for >85% of ATR binding and its expression and binding characteristics are unchanged in pregnancy (10, 11). If AT₂R is the predominant receptor in the uterine vascular bed and does not mediate ANG

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ANG II-induced smooth muscle contractions, this may explain the attenuated uteroplacental responses to infused ANG II.

Most investigators have studied uterine vascular responses to ANG II using systemic infusions of the peptide. However, it is possible that ANG II indirectly mediates these responses (3–6, 32). In the present study, we compared simultaneous uterine and systemic responses to comparable systemic and local intra-arterial ANG II infusions in pregnant and nonpregnant ewes. We postulated that systemic ANG II infusions would increase UVR in pregnant and nonpregnant ewes and that nonpregnant ewes would demonstrate increased responsiveness. We also hypothesized that uterine and systemic responses to local intra-arterial ANG II infusions would be absent or markedly attenuated in both pregnant and nonpregnant ewes.

METHODS

Animal preparation. In the present studies, we used six pregnant ewes ≥125 days of gestation (term 145 ± 5 days) and five nonpregnant oophorectomized ewes of mixed western breed. The chronically instrumented animal preparations used in these studies have previously been described (36, 37). Under general anesthesia, electromagnetic flow probes (Micron Instruments, Los Angeles, CA) were placed on both main uterine arteries (6.0- to 7.0-mm ID and 3.0- to 3.5-mm ID for pregnant and nonpregnant animals, respectively). Polyvinyl catheters filled with heparinized saline (250 U/ml) were inserted retrograde ~2.5 cm into a distal branch of the uterine artery supplying each uterine horn for local drug infusions. Polyvinyl catheters were also placed into the lower maternal abdominal aorta (the tip lying at the trifurcation) and inferior vena cava (the tip lying just below the diaphragm) via the femoral artery and vein, respectively. The ovaries were surgically removed in all nonpregnant ewes and left intact in pregnant animals. The flow probes and catheters were externalized to the flank through a subcutaneous tunnel and maintained in a canvas pouch attached to the skin with steel pins. The catheters were flushed daily with heparinized saline (250 U/ml) and closed with sterile pins. Intramuscular penicillin (600,000 U) and gentamicin (40 mg) were given on the day of surgery and the following 2 postoperative days. Each animal recovered 5–7 days prior to initiating studies. The castrated nonpregnant ewes received E2 (Sigma Chemical, St. Louis, MO) replacement, 1.0 µg/kg daily, beginning on the fourth postoperative day, but not within 24 h of a study. These studies were approved by the Institutional Review Board for Animal Research.

Experimental protocols. Two protocols were used to assess the effects of ANG II in pregnant and nonpregnant ewes. In the first, ANG II (Human; Sigma Chemical) was diluted in sterile isotonic saline to a concentration of 3 µg/ml. This solution was systemically infused at room temperature through a femoral venous catheter with a constant-infusion pump (Harvard Apparatus, South Natick, MA) using doses of 1.15, 2.29, 5.73, and 11.5 µg ANG II/min. The uterine and systemic responses to these doses of ANG II are well described (30, 37, 40) and permit us to compare the present results with prior reports from this laboratory. To compare dose responsiveness with ANG II between pregnant and nonpregnant animals, the infusion rates were corrected for weight, which averaged 67.5 ± 4.6 and 62.4 ± 8.3 kg for pregnant and nonpregnant ewes, respectively. The resulting systemic doses for pregnant and nonpregnant ewes, respectively, were 0.017, 0.034, 0.086, and 0.173 µg ANG II·min⁻¹·kg⁻¹, and 0.20, 0.25, 0.82, and 1.90 µg ANG II·min⁻¹·kg⁻¹. Doses were randomized and continuously infused over 5 min to establish steady-state responses (30, 37). There was a period of 20–30 min between doses that allowed mean arterial pressure (MAP) and UBF to return to baseline and the infused ANG II to be completely cleared from the circulation (29).

In the second protocol, ANG II was infused directly into the vascular bed of one uterine horn using the uterine artery catheter described earlier. These studies were designed to permit us to examine uterine responses in the absence of potential systemic effects. The doses of intra-arterial ANG II were determined from the estimates of steady-state arterial concentrations achieved during the continuous systemic infusion of each dose of ANG II as described by Naden et al. (29). Steady-state arterial concentration of ANG II (pg/ml) = R·infusion rate of ANG II (µg/ml)/body wt (kg)·1,000, where the constant R as determined by Naden et al. (29) for pregnant and nonpregnant ewes is 18.54 ± 2.87 (SD) and 19.85 ± 3.01 (SD), respectively. Local arterial concentrations were then obtained by varying the rate of ANG II infused in nanograms per minute while continuously monitoring UBF in that uterine horn in milliliters per minute such that estimated arterial concentration of ANG II (ng/ml) = rate of infusion (ng/min)/UBF (ml/min).

The estimated concentrations locally achieved for pregnant and nonpregnant animals were 0.4, 0.8, 2.0, and 4.0 ng/ml. Doses were randomized and continuously infused over 5 min to establish steady-state responses. As before, 20–30 min were allowed between doses so that infused ANG II could be cleared and hemodynamic parameters would return to baseline for 10 min before beginning the next infusion. We also examined the responses to 8.0 ng/ml in pregnant and nonpregnant ewes, which equates to 23 µg ANG II·min⁻¹·kg⁻¹ infused systemically. This dose, which is suprapharmacological and results in plasma levels >2,000 pg/ml, permitted us to characterize the sequence of systemic and uterine responses after overflow of locally infused ANG II into the systemic circulation. Because this is a nonphysiological dose and equivalent systemic infusions were not studied, responses are not included in either the dose-response analysis or analyses comparing differences between responses to systemic and local ANG II infusions. No animals were studied on consecutive days.

During all studies, MAP, heart rate, and UBF were continuously monitored using a six-channel pen recorder (Gould, Cleveland, OH). MAP and heart rate were monitored through a femoral arterial catheter attached to a pressure transducer (type 4–327–0109, Bell and Howell, Pasadena, CA) connected to an amplifier (model N-4307–04, Gould, Cleveland, OH). UBF was monitored with electromagnetic flowmeters (model RC-1000 or -2000, Micron Instruments, Los Angeles, CA). The flow probes have a linear response to flows in the range studied and were provided with a flow signal and zero-flow calibration. Absolute UBF measured with electromagnetic flow probes in pregnant and nonpregnant sheep compares favorably (r = 0.95) to flow measurements previously obtained in this laboratory using radioactively labeled microspheres (39) and electromagnetic flow probes (25). Baseline UBF in nonpregnant ewes ranges from 15 to 30 ml/min in each uterine horn (25, 39). Therefore, the sensitivity of the recording system was increased to quantify the changes in UBF in nonpregnant sheep (25). The data presented were obtained prior to each dose of ANG II and at 5 min of a constant systemic or local intra-arterial infusion of ANG II when a steady-state response had been established and both
MAP and UBF were stable. UVR was calculated as the MAP divided by UBF.

Statistical methods. Because basal measurements of hemodynamic variables differed between the two study groups (Table 1) and we wished to compare responses between these groups, we compared the relative changes in each variable, i.e., the percent change from baseline, which takes these differences into account. Student-Neuman-Keuls t-test was used to determine changes from baseline. Repeated-measures ANOVA was used to examine changes across doses. Two-way ANOVA was used to determine differences between responses to systemic and local ANG II infusions. Data are presented as means ± SE.

RESULTS

Basal hemodynamic data. Cardiovascular measurements obtained at the start of each study, i.e., prior to systemic or local infusions of ANG II, are summarized in Table 1. Pregnant ewes demonstrated a greater (P ≤ 0.001) basal MAP, heart rate, and UBF and a lower UVR than nonpregnant ewes.

Comparison of systemic and local infusions of ANG II in pregnant ewes. Systemic infusions of ANG II dose-dependently (P < 0.001) increased MAP (Fig. 1A) and UVR (Fig. 2A) while decreasing UBF (Fig. 3A) in pregnant ewes. The pattern of these responses was such that MAP began to rise almost immediately after initiating a systemic infusion of ANG II and achieved a steady-state pressor response by ~1 min that was maintained throughout the infusion period (Fig. 4A). This pressor response was associated with a simultaneous fall in heart rate, demonstrating an intact baroreflex in all animals (Fig. 4A). In contrast, UBF was unchanged or modestly increased during the first 2 min of infusion (Fig. 4A), after which UBF fell gradually, reaching a steady-state response by ~4 min of infusion. Thus at all doses of systemic ANG II, the fall in UBF and the calculated rise in UVR always followed the rise in MAP and the establishment of a steady-state pressor response.

In contrast to that observed with systemic ANG II infusions, local intra-arterial ANG II infusions resulted in similar arterial concentrations of the peptide in pregnant ewes; however, the changes were consistently accentuated (Fig. 5). That is, in both pregnant and nonpregnant ewes, MAP was unchanged during the initial 1.7 ± 0.2 and 2.4 ± 0.3 min of infusion, respectively, after which MAP rose rapidly to establish a steady-state increase. UBF was unchanged until 2.7 ± 0.2 and 3.6 ± 0.2 min, respectively, after the rise in MAP. Thus, as observed during systemic ANG II infusions, the fall in UBF always followed the rise in systemic blood pressure.

Comparison of systemic and local ANG II infusions in nonpregnant ewes. Systemic infusions of ANG II into nonpregnant ewes also resulted in dose-dependent rises (P ≤ 0.001) in MAP (Fig. 1B) and UVR (Fig. 2B) those observed during systemic ANG II (P < 0.0001), and the increases no longer differed among the three doses ≥2 ng/ml. The change in UVR with local ANG II (Fig. 2A) was also markedly attenuated when compared with responses seen during systemic infusions (P < 0.001), and the dose response was no longer evident.

When the pattern of response to local doses of ANG II was examined over time, UBF and UVR were minimally affected and increases in MAP were substantially delayed (Fig. 4B) compared with the almost immediate rise seen with systemic doses (Fig. 4A). This modest rise in MAP during local infusions of ANG II ≥2 ng/ml was also associated with a delayed fall in heart rate and no change or a modest rise in UBF. When we examined this using an intra-arterial dose of 8.0 ng/ml, these differences were consistently accentuated (Fig. 5). That is, in both pregnant and nonpregnant ewes, MAP was unchanged during the initial 1.7 ± 0.2 and 2.4 ± 0.3 min of infusion, respectively, after which MAP rose rapidly to establish a steady-state increase. UBF was unchanged until 2.7 ± 0.2 and 3.6 ± 0.2 min, respectively, after the rise in MAP. Thus, as observed during systemic ANG II infusions, the fall in UBF always followed the rise in systemic blood pressure.

Comparison of systemic and local ANG II infusions in nonpregnant ewes. Systemic infusions of ANG II into nonpregnant ewes also resulted in dose-dependent rises (P ≤ 0.001) in MAP (Fig. 1B) and UVR (Fig. 2B)

Table 1. Basal hemodynamic measurements in pregnant and nonpregnant ewes before systemic or local infusions of angiotensin II

<table>
<thead>
<tr>
<th></th>
<th>Pregnant (n = 23)</th>
<th>Nonpregnant (n = 74)</th>
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<tbody>
<tr>
<td>MAP, mmHg</td>
<td>93 ± 2</td>
<td>86 ± 1*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>106 ± 2</td>
<td>62 ± 2*</td>
</tr>
<tr>
<td>UVR, mmHg·min·l⁻¹</td>
<td>197 ± 16</td>
<td>3,211 ± 95*</td>
</tr>
<tr>
<td>UBF, ml/min</td>
<td>540 ± 34</td>
<td>29 ± 1*</td>
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Values are means ± SE; n, no. of measurements obtained prior to all doses of ANG II. *Differences between groups at P = 0.001 as assessed by t-test. MAP, mean arterial pressure; HR, heart rate; UVR, uterine vascular resistance; UBF, uterine blood flow.
and decreases in UBF (P < 0.001; Fig. 3B). These responses were significantly greater (P < 0.0001) than those observed in pregnant ewes at all doses of ANG II examined. In marked contrast, local intra-arterial ANG II infusions had no significant effect on MAP (P = 0.1; Fig. 1B), UVR (P = 0.3; Fig. 2B), or UBF (P = 0.08; Fig. 3B) at any dose. A dose of 8.0 ng/ml also had no significant effect on MAP, UVR, or UBF (Figs. 1B, 2B, and 3B). Therefore, all responses to local ANG II infusions in nonpregnant ewes were less (P < 0.001) at each dose compared with responses to systemic ANG II.

**DISCUSSION**

Uterine vascular responses to ANG II have generally been studied using systemic infusions of the peptide. This permits a comparison of simultaneous systemic and uterine responses (14, 30, 37) but does not allow separation of the direct effects of ANG II on the uterine vasculature from those elicited by secondary mechanisms. This is important in understanding how ANG II increases UVR, because it is known to increase sympathetic activity (3–5, 32) and endothelin release (6, 16), and the AT2R, which does not mediate contraction, accounts for >85% of ATR binding in this vascular bed in pregnant and nonpregnant women and sheep (10, 11). We, therefore, compared the effects of local and systemic ANG II infusions in pregnant and nonpregnant ewes. Intravenous ANG II dose-dependently increased MAP and UVR and decreased UBF in both groups, and responses by pregnant animals were strikingly similar to those previously reported (30, 37). However, changes in MAP as well as UVR and UBF were greater in nonpregnant versus pregnant ewes, demonstrating attenuated pressor responses during pregnancy (19, 37) and for the first time, a marked pregnancy-associated attenuation in ANG II-induced uterine vasoconstriction during systemic infusions similar to that seen with α-agonists (25). The effects of ANG II on UBF in nonpregnant ewes have not previously been examined because of the low UBF and concerns regarding the validity of these measurements. We have since demonstrated that these flow probes have excellent reliability in the range measured when the sensitivity is enhanced (25).

The difference in uterine vascular responsiveness between nonpregnant and pregnant ewes observed in the present study differs from that reported by Curran-Everett et al. (14) in gravid and nongravid guinea pigs. They infused systemic doses of ANG II similar to our two lowest doses, and although the uterine vasculature was refractory to ANG II compared with nonuterine tissues, uterine vascular responses were similar in gravid and nongravid animals. The ATR in the guinea pig uterine vasculature is not known; nonetheless, the similarity in responses and differences in uterine and nonuterine sensitivity resemble that in sheep (30, 40) and could reflect uterine artery AT2R predominance in

**Fig. 2.** Effects of comparable systemic and local intra-arterial infusions of ANG II on relative change in uterine vascular resistance in pregnant (A) and nonpregnant (B) ewes. Different letters within each group (i.e., systemic and intra-arterial) denote significant differences between responses across ANG II concentrations using repeated-measures ANOVA, P < 0.001.

**Fig. 3.** Effects of comparable systemic and local intra-arterial infusions of ANG II on relative change in uterine blood flow in pregnant (A) and nonpregnant (B) ewes. Different letters within each group (i.e., systemic and intra-arterial) denote significant differences in responses across ANG II concentrations using repeated-measures ANOVA, P < 0.001.
both groups. It is unclear, however, how resistance would be unchanged if MAP rose 30–50% and UBF was unaffected. Cohen et al. (8), studying acutely anesthetized rabbits with an isolated uterine circulation, also saw similar uterine vasoconstrictor responses to systemic ANG II in nonpregnant and pregnant animals. They, however, used a bolus of ANG II, 1 µg/kg, which exceeds by one order of magnitude the highest dose used by us and Curran-Everett et al. (14) and is not physiological. Their use of anesthetized animals further complicates comparisons with either study. Other investigators have not made similar comparisons, thus it is impossible to explain the different results other than to infer that there may be a species difference. Nonetheless, the present data suggest that the uterine vasculature, like the systemic, undergoes a significant change in sensitivity to systemic ANG II infusions during ovine pregnancy.

When we examined the effects of local intra-arterial ANG II on UBF in pregnant animals, responses were consistently less than those observed with comparable arterial concentrations during continuous systemic ANG II infusions. Furthermore, the dose response for UBF and UVR was no longer evident. In nonpregnant ewes, this difference was more obvious, e.g., 0.036 µg·min⁻¹·kg⁻¹ infused systemically decreased UBF 25 ± 8%, whereas the comparable local dose, 0.8 ng/ml, had no effect. Thus in both groups, uterine vascular responses to local ANG II were minimal or absent. Only two prior studies compared uterine vascular responses with local and systemic ANG II infusions. Cohen et al. (8) reported that local ANG II rapidly increased perfusion pressure in anesthetized nonpregnant and gravid rabbits. However, their lowest dose would have resulted in arterial concentrations >1,200 pg/ml when corrected for estimated UBF (42), which is equivalent to local concentrations >2 ng/ml. As discussed below, these doses are likely to cause systemic effects. Because minimal pressor data are presented, it is not possible to determine if a difference existed between local and systemic doses. Although they blocked uterine responses to local ANG II with saralasin, this was infused systemically, which would also inhibit any systemic effects of ANG II. Clark et al. (7) studied pregnant ewes using local intra-arterial doses similar to those in the present study. In contrast to the present and earlier studies (30, 37), systemic ANG II did not dose-dependently decrease UBF. Furthermore, while UBF fell during local ANG II infusions, especially with doses resulting in arterial concentrations >2 ng/ml, they also provided no data for simultaneous changes in either MAP or heart rate. Thus it is unclear if and when systemic responses occurred. On the basis of prior results (38), continuous intra-arterial ANG II infusions achieving levels ≥3 ng/ml would exceed the uterine clearance of ANG II in pregnant and nonpregnant ewes.

![Fig. 4. Representative recordings of simultaneous changes in mean arterial pressure, heart rate, and uterine blood flow in left and right uterine arteries of a pregnant ewe before, during, and after a continuous systemic infusion of ANG II (0.086 µg·min⁻¹·kg⁻¹; A) and a continuous local intra-arterial infusion of ANG II (4.0 ng/ml; B) via right uterine artery catheter. Bars denote location, concentration, and duration of ANG II infusions. BPM, beats/min.](http://ajpregu.physiology.org/DownloadedFrom/)
in systemic blood pressure, suggesting that uterine vascular responses to ANG II might be indirect, i.e., due to systemic effects of infused ANG II.

Evidence for an indirect effect of ANG II on the uterine vascular bed is further supported by estimating the systemic plasma levels achieved during local infusions. The ovine uteroplacental bed clears ~20% of infused ANG II (38); thus a continuous infusion resulting in 0.4 ng/ml would result in systemic plasma levels of ~23 pg/ml when UBF is 500 ml/min and cardiac output is 7 l/min. When local arterial concentrations are increased 10-fold, 4.0 ng/ml, the estimated systemic arterial level is ~229 pg/ml. The former has no effect on MAP, but the latter increases MAP ~20% (30, 37). In the present study, this dose, infused locally in pregnant ewes, increased MAP 23 ± 6%. This also explains the even greater rise in MAP seen with the highest local dose of ANG II studied, 8.0 ng/ml. In the case of nonpregnant ewes, UBF was 5% of that in pregnant animals; thus the total ANG II dose infused was quite small compared with the pregnant sheep, and overflow of ANG II into the systemic circulation would also be quite small, explaining the minimal pressor response observed during local infusions (see Fig. 1).

Local ANG II may have had minor effects directly on UVR, possibly reflecting the 15% of AT$_1$R present in uterine artery smooth muscle (10), but the rise in UVR was consistently less than the rise in MAP. Therefore, decreases in UBF were of minor consequence. Human uterine artery smooth muscle also expresses ≥15% AT$_1$R (11), and ANG II contracts human uterine arteries in vitro (20, 33). These responses, however, are substantially less than those elicited with an $\alpha$-agonist or KCl. Thus, whereas ANG II may have a small direct effect, systemic ANG II may have mediated release of another more potent uterine vasoconstrictor. For example, ANG II induces adrenal medullary catecholamine release through a receptor-mediated mechanism (4, 32), and the uterine vascular bed in intact nonpregnant and pregnant ewes is far more sensitive to $\alpha$-agonists than the systemic vasculature (1, 25, 31, 41). Thus $\alpha$-agonists can decrease UBF and increase UVR without altering MAP (25, 41). The uterine vascular bed, however, develops refractoriness to infused $\alpha$-agonists in ovine pregnancy (25), suggesting that local mechanisms are able to modify uterine vascular responses to these and other vasoconstrictors. These mechanisms appear to be multiple and may include enhanced basal synthesis of endothelium-derived prostacyclin (24), ANG II-mediated increases in endothelium-derived prostacyclin via activation of endothelial AT$_1$R (10, 24, 26), and, possibly, increases in basal and stimulated uterine artery NO production (28). Evidence that prostacyclin is involved can be obtained from the observation that local cyclooxygenase inhibition increases uterine vascular sensitivity to systemic ANG II across a range of doses (27). Although ANG II-mediated adrenal catecholamine release could account for the effects of systemic ANG II on the uterine circulation, other considerations include increases in sympathetic outflow (3), alterations in reuptake of catecholamines (5), and altered

![Fig. 5. Representative recordings of simultaneous changes in mean arterial pressure, heart rate, and uterine blood flow in left and right uterine arteries of a pregnant ewe before, during, and after continuous local intra-arterial infusion of a pharmacological dose of ANG II, 8.0 ng/ml, via right uterine artery catheter. This dose was used to characterize delays in pressor response and subsequent fall in blood flow associated with local ANG II infusions. Bar denotes location, concentration, and duration of ANG II infusions.](http://ajpregu.physiology.org/doi/abs/10.1152/ajpregu.00342.2017)
orthostatic hypotension) or activation of the sympathetic nervous system. It now appears evident that several mechanisms serve to protect the uteroplacental vascular bed from the persistent rise in plasma ANG II that is altered in women with pregnancy-induced hypertension (8). These mechanisms include a predominance of AT$_2$R in uterine vascular smooth muscle, AT$_1$R-mediated increases in endothelium-derived prostacyclin (and possibly NO), and substantial increases in basal arterial synthesis of prostacyclin and NO. It is possible that one or more of these mechanisms is altered in women with pregnancy-induced hypertension, resulting in the fall in UBF associated with this pathologic process and the rise in fetal and neonatal morbidity often seen.

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Address for reprint requests and other correspondence: B. E. Cox, Dept. of Pediatrics, Univ. of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX 75235–9063 (E-mail: BCOX@smued.net).

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