Effect of gestational stage on uterine artery blood flow during exercise in rabbits

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Effect of gestational stage on uterine artery blood flow during exercise in rabbits. J Appl Physiol 99: 2159–2165, 2005. First published August 18, 2005; doi:10.1152/japplphysiol.00236.2005.—We tested the hypothesis that the uterine artery vasoconstrictor response to exercise during early gestation would be similar to the nonpregnant (NP) state and would be attenuated at mid and term gestation. Responses to graded treadmill exercise were measured in six female New Zealand White rabbits in the NP state and at day 10, day 20, and day 28 (term) of gestation. Uterine artery blood flow (UtBF) was measured continuously with a Transonic flow probe. Rabbits performed a graded exercise test to voluntary exhaustion (maximal exercise) starting at 7 m/min, 7% grade. UtBF and uterine artery conductance (UtC) decreased similarly during graded exercise (P < 0.01) in the NP state [at maximal exercise: −40% (SD 20) for UtBF and −45% (SD 14) for UtC] and at day 10 of gestation [at maximal exercise: −48% (SD 17) for UtBF; −56% (SD 14) for UtC]. In contrast, there was little change in UtBF or UtC during graded exercise at day 20 [at maximal exercise: −4% (SD 17) for UtBF, P < 0.05 vs. NP; −16% (SD 12) for UtC, P < 0.01 vs. NP] and at day 28 [At maximal exercise: +7% (SD 15) for UtBF, P < 0.01 vs. NP; −2% (SD 24) for UtC, P < 0.01 vs. NP], indicating substantial attenuation of the uterine artery vasoconstrictor response to exercise. At rest, UtC responses to graded doses of intravenous phenylephrine were unaffected by the stage of gestation, which suggests that uterine artery responsiveness to α1-adrenoreceptor stimulation is preserved throughout gestation. Normal pregnancy in the rabbit is associated with attenuation of the uterine artery vasoconstrictor response to graded exercise that develops by mid gestation.

A PHYSICALLY ACTIVE LIFESTYLE is recommended for women with normal pregnancies, whereas exercise remains an absolute contraindication for women with pregnancies complicated by superimposed hypertensive conditions or intrauterine growth restriction (1, 14). During dynamic exercise in the nonpregnant state, blood flow is preferentially delivered to active skeletal muscle and shunted away from visceral organs (21, 40). During pregnancy, resting blood flow to the uterus increases throughout the gestational period to supply oxygen, glucose, and other nutrients to meet the metabolic needs of the developing fetus (26, 28). Because nutrient delivery to the placenta is one factor that impacts fetoplacental growth (11, 26), of continued interest is the control of the uterine circulation during pregnancy when faced with an acute stressor, such as exercise, that is known to initiate vasoconstriction in and reduce blood flow to visceral organs. A greater understanding of uterine circulatory control during normal pregnancy may provide insight on mechanisms underlying the exaggerated vasoconstrictor response observed immediately postexercise in pregnancies complicated by preeclampsia and/or intrauterine growth restriction (20).

A clear understanding of the quantitative relationship between exercise intensity and uterine blood flow responses during normal pregnancy in women is still lacking because of an inability to accurately image uterine artery blood flow during dynamic exercise. Most data in women have been obtained after the 30th wk of gestation (3rd trimester). At this time in gestation, data obtained from Doppler ultrasonography of the uterine artery immediately after cessation of exercise indicated that uterine vascular resistance increases (16, 20, 30) or changes little (24, 29) in response to brief, dynamic exercise.

It is known that submaximal dynamic exercise produces mild to moderate (<30%) reductions in uterine artery blood flow in treadmill-exercised pregnant sheep (27), pregnant rats (15), and pregnant goats (23). Recently, our laboratory (34) reported that in the term-pregnant rabbit, the exercise-related decrease in uterine artery blood flow (UtBF) and uterine artery conductance (UtC) were mild and considerably attenuated compared with the uterine artery vasoconstrictor responses observed in the nonpregnant state. These observations suggest that adaptations in uterine circulatory structure and/or functional control present in late gestation limit the redistribution of uterine blood flow during dynamic exercise.

The uterine circulation undergoes enlargement and remodeling during the gestational period as the uteroplacental circulation becomes established in the first half of gestation and fetal growth progresses (2, 9, 10). Chemical and neural control of the uterine vasculature may also depend on the stage of gestation (22, 25). In the gravid rabbit, increases in fetal growth and placental blood flow accelerate beginning at ~day 20 of a 31-day gestation (3). Thus it is of interest to determine in the rabbit whether the attenuation of exercise-related uterine vasoconstriction extends to the mid-gestational period, which marks the beginning of rapid fetal growth.

Thus we hypothesized that in the rabbit, gestational attenuation of the uterine artery vasoconstrictor response to exercise would be evident at mid gestation (day 20) but not in early gestation (day 10). We utilized rabbits chronically instrumented with a uterine artery flow probe to investigate the uterine artery circulatory response to a treadmill graded exercise test to voluntary exhaustion in the nonpregnant state and at early (day 10), mid (day 20), and term (day 28 of an ~31 day) gestation. In addition, at each stage of gestation we evaluated...
at rest the uterine artery vasoconstrictor response to the α1-adrenoreceptor agonist, phenylephrine (PE), to evaluate the hypothesis that reduced uterine vascular α-adrenoreceptor sensitivity may be one mechanism that contributes to the gestational attenuation of uterine artery vasoconstriction during exercise in the rabbit.

METHODS

The experimental and animal care protocols were reviewed and approved by the Research and Animal Care Committee of Midwestern University. Six female New Zealand White rabbits of breeding age were selected for willingness to run on a motor-driven treadmill (AccuScan, Columbus, OH) that had a usable belt length of 1 m. After selection and before surgical preparation, the rabbits were exercised once a week to maintain familiarity with the treadmill. The number of presurgical exercise sessions ranged from 2 to 13 (median = 4). The familiarization sessions were conducted on a 7% grade and consisted of a continuous graded exercise bout of 3 min at 7 m/min, 2 min at 10 m/min, 2 min at 13 m/min, and 2 min at 16 m/min.

Experimental design. The experimental design called for each animal to be studied at four time points: in the nonpregnant state and at early, mid, and term gestation. We defined early gestation as day 10, mid gestation as day 20, and term gestation as day 28 of an ~31-day gestation. Rabbits were bred in-house with a proven buck.

Rabbits were chronically instrumented with one or two ultrasonic transit-time flow probes (1.0–1.5 mm R series; Transonic Systems, Ithaca, NY) on the left and/or right uterine artery. Three animals were instrumented with a single flow probe. Because of requirements of a concurrent study, three of the remaining rabbits were instrumented with two flow probes, which were placed on the right and left uterine arteries, followed by a unilateral oviduct ligation. In all three animals, we received adequate flow signals from the flow probe on the uterine artery that supplied the uterine horn associated with the intact oviduct. The data received from the contralateral flow probe are not reported here.

Surgical preparation. Rabbits were anesthetized with Telazol (tiletamine hydrochloride and zolazepam hydrochloride; 15 mg/kg im; Fort Dodge, Fort Dodge, IA) and xylazine (xylazine hydrochloride 5 mg/kg im; Butler, Columbus, OH), given Baytril (enrofloxacin 5 mg/kg sc; Bayer, Shawnee Mission, KS) as a prophylactic antibiotic, and intubated with a cuffed endotracheal tube. To maintain a surgical plane of anesthesia, the rabbits were mechanically ventilated with 2.5–3.0% isoflurane with oxygen supplementation. Buprenex (buprenorphine hydrochloride 0.03 mg/kg sc; Reckitt Benckiser Pharmaceuticals, Richmond, VA) was given immediately and 5–8 h postoperatively for pain management.

Implantation of uterine artery flow probe. Rabbits were chronically instrumented with uterine artery flow probe(s) via a midline lower abdominal incision. The rabbit has a bicornate uterus. A uterine horn receives arterial blood flow from an ipsilateral uterine artery and a small contribution from the ipsilateral ovarian artery to the lateral end of the uterine horn (6); thus the flow signal we received from the uterine artery represented the majority of the flow to the uterus and fetoplacental units in the ipsilateral horn. The artery-probe complex was wrapped with a small piece of medical-grade silicone elastomer (Technical Products of Georgia, Decatur, GA) to stabilize the probe orientation and avoid trapping adipose tissue in the reflecting bracket during the ingrowth phase. A small amount of Kwik-Cast (World Precision Instruments, Sarasota, FL) was applied around the base of the flow probe to secure the position of the probe. The free end of the flow probe was mounted to a skin button or was stored in a small plastic box (with a hinged top) sutured to the skin on the animal’s back. At least 14 days separated the flow probe surgery and the first (nonpregnant) exercise trial.

Acute instrumentation and data collection. On the day of the experiment, the rabbit was brought to the laboratory. The skin overlying the central ear artery and marginal vein was anesthetized with topical EMLA cream (lidocaine 2.5% and prilocaine 2.5%; Astra, Westborough, MA). Arterial blood pressure (BP) was obtained from a small Teflon catheter (Angiocath 24 gauge (OD = 0.7 mm), Becton Dickinson, Sandy, UT) placed into the central ear artery by percutaneous placement. The arterial catheter was connected to a solid-state pressure transducer that was strapped to the rabbit’s back. Venous access was obtained by percutaneous placement of a 24-gauge Teflon catheter into the contralateral ear vein. The free end of the uterine artery flow probe was connected by a 2-m extension cable to the Transonic flowmeter (model T206) for measurement of UtBF. Pulsa
ticle BP and UtBF signals were continuously acquired and stored during each data collection period using a PowerLab 8SP system and Chart 4.0 software (ADInstruments, Mountain View, CA). Heart rate (HR) was derived from the arterial pressure pulse, and UtC was calculated in real time from the pulsatile UtBF and BP signals [UtBF (in ml/min)/ BP (in mmHg)]. Mean values for BP, HR, UtBF, and UtC were obtained by averaging the continuous waveforms over specified time intervals (see Data analysis below). Conductance and the percent change in conductance have been shown to be better indicators of the vasocostrictor response to exercise compared with resistance when assessing a wide variety of baseline flows and high-flow states (4, 36). For this reason, we used UtC and the percent change in UtC as indicators of the vasocostrictor responses to PE and graded exercise.

Experimental protocol. Rabbits underwent the same experimental protocol in the nonpregnant state and at days 10, 20, and 28 of gestation. While resting quietly in the transport box and after at least 30 min elapsed after acute instrumentation with ear arterial and venous lines (described above), we administered three doses of PE intravenously (0.5, 1.5, and 2.5 μg/kg) to evaluate the uterine vascular response to α1-adrenoreceptor stimulation. The dose order was alternated among animals, and at least 5 min separated each dose.

At least 15 min elapsed after the PE dose-response series before the rabbit underwent the maximal graded exercise test. Data were collected while the rabbit was sitting (rest) or hopping (exercise) on the treadmill. The treadmill grade was set at 7%. After 2 min of data collection at rest on the treadmill, the rabbit exercised to voluntary exhaustion using the following protocol: 3 min at 7 m/min and then 2 min each at 10, 13, 16, 20, 22 m/min or to exhaustion. Rabbits were encouraged to continue running by a gentle push from the investigator’s hand. Exhaustion was defined as failure to maintain pace with the treadmill belt. The final stage must have been 20 s in length to be included in the analysis. Exhaustion occurred at 20–22 m/min in the nonpregnant state and at 13–22 m/min during pregnancy. In five of the six animals completing the exercise test at term gestation, the final treadmill speed was one (in 3 animals) to two (in 2 animals) stages lower than the final speed achieved in the nonpregnant state.

After completion of the experiment on day 28 of pregnancy, five of the six gravid rabbits were euthanized with an intravenous overdose of a pentobarbital sodium solution (Sleepaway, Fort Dodge Animal Health, Fort Dodge, IA). The uterus was exposed via a midline incision, and the euthanized fetuses were retrieved. Based on their size, coloration, and morphology, fetuses were labeled as either potentially viable or nonviable at the time of euthanization. The sixth rabbit was returned to her cage and spontaneously delivered nine live neonates on day 31. Neonates were euthanized with an intraperitoneal overdose of the euthanizing solution.

Data analysis. Rest data for the exercise tests are represented by a 2-min average and the rest data for the PE dose-response tests are represented by a 30-s average. The physiological responses to bolus PE administration were averaged in consecutive 2-s intervals and the maximal change in variables was selected at each dose of PE. Physiological responses at each treadmill speed during the graded exercise test are represented by a 30-s average collected at the end of

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each stage, with the exception of one trial in which the final exercise stage contained 24 s of usable data.

A repeated-measures analysis using a general linear model (SPSS 12.0, SPSS, Chicago, IL) was used to analyze responses to exercise or to administration of PE. The main effects included stage of gestation, exercise intensity and/or dose of PE. A Dunnett’s t-test (18) was used to compare the control or first level (nonpregnant or rest) to subsequent levels of gestation or exercise intensity. Pairwise comparisons among the three doses of PE were completed using the Bonferroni t-test. A paired t-test was utilized to compare body weights between the nonpregnant and term-pregnant conditions. Linear regression analysis was utilized to examine the relationship between relative exercise intensity (expressed as a % of maximum exercise HR) and relative changes in UtBF or UtC with exercise at each stage of gestation. Data are represented as means (SD).

RESULTS

Animal weights increased from 3.6 kg (SD 0.4) during the non-pregnant state to 4.1 kg (SD 0.4) at term gestation (P < 0.01). The number of live fetuses carried by each dam ranged from four to nine, with a median of seven and average fetal weight of 44 g (SD 9). One dam presented with five viable fetuses with an average weight of 42 g (SD 7) accompanied by five small (nonviable) fetuses with weights ≤4 g. The small fetuses were found in both uterine horns.

BP and HR. The BP and HR values at rest and during graded exercise are shown in Fig. 1. BP at rest [NP: 75 mmHg (SD 7)] was not significantly altered in pregnancy. BP increased in response to graded exercise (P < 0.001), and the stage of gestation did not affect this response.
In the nonpregnant state, HR before exercise was 268 beats/min (SD 21) and did not vary significantly over gestation. HR increased in response to graded exercise ($P < 0.001$) regardless of pregnancy status. However, there was an interaction between stage of gestation and exercise intensity ($P < 0.01$) that manifested as a reduction in maximal HR achieved [nonpregnant: 401 beats/min (SD 25)] during the exercise test at day 10 [380 beats/min (SD 38); $P < 0.01$], day 20 [383 beats/min (SD 21), $P = 0.05$], and day 28 [380 beats/min (SD 21); $P < 0.01$] of gestation.

**UtBF and UtC.** The absolute UtBF and UtC values at rest and during graded exercise are shown in Fig. 1. In the nonpregnant state, UtBF before exercise was 3 ml/min (SD 2). UtBF before exercise was elevated as early as day 10 ($P < 0.01$) and continued to increase through day 20 ($P < 0.01$) and day 28 [25 ml/min (SD 7); $P < 0.01$] of gestation. In the nonpregnant state, UtBF decreased during graded exercise (Fig. 1; $P < 0.01$), and the relative change at maximal exercise was $-40\%$ (SD 20). At day 10 of gestation, the UtBF response to graded exercise [% change at maximal exercise was $-48\%$ (SD 17)] was similar to the response observed in the nonpregnant state. In contrast, there was little change in UtBF during graded exercise during the latter half of gestation (Fig. 1). The relative change in UtBF at maximal exercise at day 20 was $-4\%$ (SD 17) ($P < 0.05$ vs. nonpregnant) and at term gestation was $+7\%$ (SD 15) ($P < 0.01$ vs. nonpregnant), indicating a substantial attenuation of the UtBF response to exercise with advancing gestation.

In the nonpregnant state, UtC before exercise was 4 ml·min$^{-1}·$mmHg$^{-1}$ (SD 2). Similar to UtBF, UtC before exercise was elevated as early as day 10 ($P < 0.05$) and continued to increase through day 20 ($P < 0.01$) and day 28 [38 ml/min (SD 13); $P < 0.01$] of gestation. In the nonpregnant state, UtC decreased during graded exercise ($P < 0.01$) and the relative change in UtC at maximal exercise was $-45\%$ (SD 14). At day 10 of gestation, the UtC response to graded exercise [% change at maximal exercise was $-56\%$ (SD 14)] was similar to the response in the nonpregnant state. In contrast, at day 20 of gestation, the UtC response to exercise was minor ($P = 0.053$) at day 20 of gestation and was absent ($P = 0.2$) at term gestation. As seen with UtBF, the relative changes in UtC at maximal exercise were greatly attenuated ($P < 0.01$ for days 20 and 28) compared with the nonpregnant state [day 20, $-16\%$ (SD 12); day 28, $-2\%$ (SD 24)].

In Fig. 2, the relative decreases in UtBF and UtC for each animal at each stage of gestation are plotted vs. exercise intensity expressed as relative (%) to maximum exercise heart rate (MHR). Plots are shown for NP vs. day 10 (left), day 20 (middle), and day 28 (right) of gestation. Linear regression line is superimposed on the scatterplot for each group. Linear regression equations and ANOVA results follow. NP: %change UtBF = $-1.18 \times %MHR + 69$, $R^2 = 0.14$, $P = 0.03$; %change UtC = $-1.01 \times %MHR + 55$, $R^2 = 0.16$, $P = 0.024$. Day 10: %change UtBF = $-1.28 \times %MHR + 82$, $R^2 = 0.22$, $P = 0.008$; %change UtC = $-0.37 \times %MHR + 23$, $R^2 = 0.03$, $P = 0.4$. Day 20: %change UtBF = $-0.46 \times %MHR + 43$, $R^2 = 0.04$, $P = 0.3$; %change UtC = $-0.37 \times %MHR + 23$, $R^2 = 0.03$, $P = 0.4$. Day 28: %change UtBF = $0.24 \times %MHR - 15$, $R^2 < 0.01$, $P = 0.7$; %change UtC = $0.52 \times %MHR - 51$, $R^2 = 0.01$, $P = 0.6$. 

Fig. 2. Scatterplots of the relative change in UtBF (%change UtBF; top) and UtC (%change UtC; bottom) vs. exercise intensity expressed as relative (%) to maximum exercise heart rate (MHR). Plots are shown for NP vs. day 10 (left), day 20 (middle), and day 28 (right) of gestation. Linear regression line is superimposed on the scatterplot for each group. Linear regression equations and ANOVA results follow. NP: %change UtBF = $-1.18 \times %MHR + 69$, $R^2 = 0.14$, $P = 0.03$; %change UtC = $-1.01 \times %MHR + 55$, $R^2 = 0.16$, $P = 0.024$. Day 10: %change UtBF = $-1.28 \times %MHR + 82$, $R^2 = 0.22$, $P = 0.008$; %change UtC = $-0.37 \times %MHR + 23$, $R^2 = 0.03$, $P = 0.4$. Day 20: %change UtBF = $-0.46 \times %MHR + 43$, $R^2 = 0.04$, $P = 0.3$; %change UtC = $-0.37 \times %MHR + 23$, $R^2 = 0.03$, $P = 0.4$. Day 28: %change UtBF = $0.24 \times %MHR - 15$, $R^2 < 0.01$, $P = 0.7$; %change UtC = $0.52 \times %MHR - 51$, $R^2 = 0.01$, $P = 0.6$. 

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intensity expressed as a percentage of maximum HR, to account for the possibility that the similar absolute exercise intensity (i.e., treadmill speed) represented a greater relative intensity as gestation progressed. In the nonpregnant state, increases in exercise intensity from 76 to 100% of maximum HR resulted in progressive decreases in UtBF ($R^2 = 0.14; P = 0.03$) and UtC ($R^2 = 0.16; P = 0.02$). Similar results were obtained early in gestation for UtBF ($R^2 = 0.22; P = 0.008$) and UtC ($R^2 = 0.24; P = 0.005$). As shown in Fig. 2 (middle and right), the relationship between the relative change in UtBF or UtC and relative exercise intensity was absent during the latter half of gestation.

UtC response to PE. As depicted in Fig. 3, graded bolus intravenous doses of the $\alpha_1$-adrenergic agonist PE elicited progressively greater relative decreases in UtC ($P < 0.001$). In the nonpregnant state, the reduction in UtC ranged from $-29\%$ (SD 10) at 0.5 $\mu$g/kg to $-77\%$ (SD 21) at 2.5 $\mu$g/kg. There was no effect of pregnancy on the vasoconstrictor response to PE ($P = 0.67$).

DISCUSSION

In this study, chronically instrumented rabbits were utilized to make continuous measurements of UtBF during a maximal graded exercise test in the nonpregnant state and at early (day 10), mid (day 20), and term gestation (day 28). The major findings of this study were that 1) the uterine artery vasoconstrictor response to exercise present in the nonpregnant state was affected little in early gestation but was substantially attenuated at mid gestation and absent at late gestation, 2) the relationship between relative exercise intensity and the uterine vasoconstrictor response apparent in the nonpregnant state was absent at mid and late gestation, and 3) the uterine vasoconstrictor response to acute stimulation of $\alpha_1$-adrenergic receptors with PE was unaffected during pregnancy.

Studies on near-term-pregnant sheep, rats, and pygmy goats have documented reductions in UtBF during treadmill exercise (15, 23, 27). Only in the rat are there data comparing uterine blood flow values during exercise at different points in gestation. In a cross-sectional study, Dowell and Kauer (15) used microspheres to measure uterine blood flow during treadmill exercise in rats at days 15 and 22 of a 22-day gestation. In the pregnant rats, absolute uterine blood flow during exercise did not change at day 15 of gestation, but it decreased by $\sim 30\%$ during exercise at term compared with resting levels. These results suggest that in the exercising rat advancing gestation resulted in a greater rise in uterine vascular resistance during exercise. These data contrast with our observations that the latter half of pregnancy in the rabbit is associated with a blunted reduction in UtBF and UtC during graded exercise.

In rabbits, the attenuated uterine artery vasoconstrictor response to dynamic exercise may be a protective mechanism. As discussed by Gilbert et al. (17), the uterus in the term-pregnant rabbit has a relatively high oxygen extraction (60–74% compared with 24% in the sheep) at rest, and arterial oxygen content in the rabbit is lower at term than at mid gestation. With a limited ability to increase oxygen extraction, defense of UtBF during sustained activity in the gravid rabbit may be an important strategy in maintaining adequate oxygen delivery to the fetuses.

Doppler ultrasonography of a uterine artery has been used to evaluate the uterine circulatory response to exercise in third trimester-pregnant women. These studies report no change (24, 29) or increases in uterine artery resistance (16, 20, 30) immediately after submaximal exercise. It is not clear whether the uterine artery circulatory response to exercise in women differs as gestation advances. Clapp et al. (12) performed serial ultrasound measurements throughout pregnancy of the portal vein blood flow response during exercise. Measurements were taken immediately after 20 min of moderate treadmill exercise. Exercise reduced portal vein blood flow at each stage of gestation. The relative decrease from standing rest was somewhat higher at 16 wk ($\sim 76\%$) compared with 26 and 36 wk of gestation ($\sim 67\%$). To the extent that portal vein flow responses qualitatively reflect the response of the uteroplacental circulatory bed during exercise, these data leave open the possibility that advanced gestation in women is normally associated with an attenuation of uterine vasoconstriction during submaximal exercise.

Physiological mechanisms that could contribute to the blunted uterine vasoconstrictor response to exercise observed at mid and term gestation in the rabbit include progressive perivascular adrenergic denervation, altered adrenergic receptor function, and enhanced endothelial vasodilator production.

In the nonpregnant rabbit, the uterine blood vessels and myometrium are innervated by sympathetic adrenergic nerves (5). Large decreases in uterine artery vascular noradrenaline content (31) and in the density of perivascular adrenergic innervation in myometrial tissue (25, 39) have been noted in the latter half of human and animal pregnancy. In pregnant rats, degeneration of adrenergic nerves occurs in the myometrium and at perivascular sites (25). Compared with the nonpregnant state, the denervation process was apparent at mid gestation and continued to progress toward term gestation. The density of adrenergic innervation is also decreased in uterine veins in late pregnant rats (37). This pattern of denervation in the pregnant rat would be consistent with the mid- to late-gestational attenuation of the uterine artery vasoconstrictor response to exercise observed in the rabbit.
Despite the extensive denervation of the uterus associated with pregnancy in the rabbit (39), it is unlikely that functional sympathetic control of the uterine vasculature has been abrogated. Activation of the nasopharyngeal reflex (35, 44), which is known to strongly activate sympathetic nerves to visceral organs, results in an ~87% decrease in uterine artery conductance in the term-pregnant rabbit (34). These data imply that residual perivascular uterine sympathetic innervation is present and is capable of being reflexively activated in the pregnant rabbit. Utilizing electrical field stimulation, Nelson et al. (31) found that whereas neurogenic constriction of human uterine artery was reduced in pregnancy, it was still clearly present and frequency dependent. While it is clear that advancing pregnancy in rabbits is associated with altered baroreflex control of HR and renal sympathetic nerve activity at rest (35, 38), it is presently unknown whether pregnancy alters the central control of the residual uterine sympathetic nerves. A decrease in uterine sympathetic neural activation in response to dynamic exercise would contribute to the blunted uterine artery vasoconstriction we observed at mid and term gestation in the rabbit.

Reduced vascular $\alpha_1$-adrenoreceptor responsiveness is another potential mechanism that could contribute to the blunted uterine artery vasoconstrictor response to graded exercise during pregnancy. However, enthusiasm for this hypothesis is tempered by studies in isolated uterine arteries that indicate that the vascular response to $\alpha_1$-adrenoreceptor stimulation with PE is enhanced in rat pregnancy (13, 43). In human uterine artery examined in vitro, maximal contractile response and sensitivity to exogenous norepinephrine were unaffected by pregnancy (42). In the present study, we found that in conscious rabbits, the relative decrease in UtIC with acute stimulation of $\alpha_1$-adrenoreceptors with PE was not substantially modified during pregnancy. These in vitro and in vivo data indicate that at rest (or in the basal state in isolated tissue) that the $\alpha_1$-adrenoreceptor-mediated contractile response in the uterine vasculature is at least well preserved and possibly enhanced during pregnancy. In light of these data, if there is a contribution of reduced $\alpha_1$-adrenoreceptor-mediated constriction to uterine vascular control during dynamic exercise in pregnancy, it is likely induced by the exercise state and must be transient in nature.

Accordingly, a complementary hypothesis to consider is that enhanced vasodilator production during exercise contributes to the blunted uterine vasoconstrictor response to graded exercise in the latter half of pregnancy in the rabbit. It is understood that basal endothelial production of nitric oxide in uterine artery is elevated in pregnancy in animals and humans (32, 41). Ni et al. (33) documented in isolated rat uterine arcuate artery that endothelial-dependent vasodilation was enhanced at term pregnancy under conditions of $\alpha_1$-adrenoreceptor precontraction and acetylcholine stimulation. Wang et al. (43), working with rat uterine radial arteries, found that term pregnancy potentiated endothelial-dependent relaxation to $\alpha_2$-adrenoreceptor stimulation with the agonist clonidine. Results from electrical field stimulation of isolated human uterine artery led Nelson et al. (31) to conclude that enhanced neurogenic vasodilation, mediated by nitric oxide and possibly calcitonin gene-related peptide, could contribute to neurogenic vascular control in pregnancy. Thus an enhanced endothelial-dependent vasodilator response to the alterations in circulating catecholamines or shear stress associated with exercise, accompanied by a shift in the ratio of adrenergic to nonadrenergic, noncholinergic innervation of the uterine resistance vasculature, are plausible factors that could contribute to the blunted uterine vasoconstrictor response during exercise in mid to late pregnancy.

Exposure to chemical factors released by the placenta and/or fetus could modify the uterine vascular response to dynamic exercise. That attenuation of the uterine vasoconstrictor response to exercise in the rabbit manifests in the latter half of gestation, which is the time of rapid fetal growth (3), supports the hypothesis that this alteration in uterine vascular control may be influenced by signals originating from the fetoplacental unit. Osol and colleagues have hypothesized that the differential remodeling of the arterial vasculature supplying placental vs. myometrial sites that they have observed in the rat (19) and rabbit (10) is due to local action of chemical factors derived from the fetoplacental unit. Recently, this group has provided evidence in the rat that venoarterial communication (transfer of small molecules across the venous wall to the adjacent artery) can occur in vitro in uterine vessels (7) and that uterine vein wall permeability is affected by gestation (8). Further study is necessary to examine the possible role of placental- and/or fetal-derived factors, acting either locally via venoarterial communication or as circulating hormones, as regulators of the uterine vascular response to dynamic exercise.

Summary. These data from rabbits indicate that the normal uterine artery vasoconstrictor response to dynamic exercise is attenuated at mid gestation and is absent at term gestation, suggesting that exercise-induced redistribution of blood flow away from the uterus is blunted during the latter half of normal gestation in rabbits. Because the uterine artery vasoconstrictor response to $\alpha_1$-adrenoreceptor stimulation with infused PE at rest was unchanged with pregnancy, it is unlikely that this gestational attenuation of the uterine artery vasoconstrictor response to dynamic exercise in the rabbit is primarily due to a reduction in uterine vascular sensitivity to circulating or neurally derived catecholamines.

GRANTS
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REFERENCES
EXERCISE IN RABBIT PREGNANCY