Disproportionate Decrease in $\alpha$- Compared With $\beta$-Adrenergic Sensitivity in the Dorsal Hand Vein in Pregnancy Favors Vasodilation

Ruth Landau, MD; Victor Dishy, MD; Alastair J.J. Wood, MD; C. Michael Stein, MD; Richard M. Smiley, MD, PhD

Background—Altered vascular responses to adrenergic agonists during pregnancy are thought to play an important role in the regulation of blood pressure and placental blood flow. Because $\alpha_1$-adrenergic and $\beta_2$-adrenergic sensitivity act in opposing directions to determine vascular tone, we simultaneously evaluated $\alpha$-adrenergic–mediated vasoconstriction and $\beta$-adrenergic–mediated vasodilation in dorsal hand veins during and after pregnancy.

Methods and Results—Twenty healthy pregnant women were studied at 32 to 37 weeks of gestation and again 12 weeks after delivery. Vascular response to phenylephrine (PE) and isoproterenol (ISO) was measured in a dorsal hand vein using the linear variable differential transformer technique. The dose of PE resulting in 50% constriction ($CD_{50}$) was determined. The response to ISO was measured after the PE preconstriction. Pregnant and postpartum values, expressed as geometric mean (95% CI), were compared by paired $t$ test. $\alpha$-Adrenergic sensitivity during pregnancy ($CD_{50}$, 2.7 $\mu$g/min [95% CI, 1.5 to 5.0]) was markedly decreased, 7-fold, compared with postpartum (0.4 $\mu$g/min [95% CI, 0.3 to 0.7] [$P<0.01$]). $\beta$-Adrenergic vasodilation was also attenuated during pregnancy. The $ED_{50}$ of ISO (dose of ISO resulting in 50% of the maximal response, $E_{max}$) was greater during pregnancy (20 ng/min [95% CI, 11 to 35]) than postpartum (8 ng/min [95% CI, 5 to 12]) ($P<0.05$). ISO $E_{max}$ was also significantly less during pregnancy (81% [95% CI, 65 to 97]) compared with postpartum (105% [95% CI, 97 to 113]) ($P<0.01$).

Conclusions—Normal pregnancy is characterized by decreased venous sensitivity to both $\alpha_1$-adrenoceptor–mediated vasoconstriction and $\beta_2$-adrenoceptor–mediated vasodilation. The greater decrease in $\alpha_1$ compared with $\beta_2$ response may contribute to the vasodilated state characteristic of human pregnancy. (Circulation. 2002;106:1116-1120.)

Key Words receptors, adrenergic, alpha $\square$ receptors, adrenergic, beta $\square$ veins $\square$ pregnancy $\square$ vasoconstriction

Intravascular volume is increased substantially in normal pregnancy and is accompanied by decreased arterial and venous tone and blunted vascular responses to vasoconstricting drugs and hormones. Although the alterations in vascular tone and volume are necessary adaptations to the pregnant state, the molecular mechanisms underlying these hemodynamic changes are poorly understood and characterized. It is commonly stated that pregnant women have a diminished response to vasoconstricting and vasodilating drugs and endogenous vasoactive substances, but this phenomenon and its magnitude have rarely been demonstrated in vivo. The dorsal hand-vein technique with a linear variable differential transformer (LVDT) allows the direct, in vivo assessment of vascular responses to a variety of agents. By using low doses of drugs acting primarily at the local segment of the vessel under study, systemic effects and the consequent reflex responses that occur after systemic administration of large doses of vasoactive drugs are avoided, making it a particularly attractive method for studying vascular sensitivity during pregnancy. We used the LVDT dorsal hand-vein technique, with infusion of micro-doses of agonists to determine and compare $\alpha$- and $\beta$-adrenergic vascular sensitivity during normal pregnancy and postpartum.

Methods

After Institutional Review Board approval and informed written consent, 20 healthy pregnant women were studied. All women were undergoing uncomplicated, singleton pregnancies with no history of significant medical disease or pregnancy-induced hypertension and were taking no medications with the exception of prenatal vitamins. Subjects were studied twice; first between 32 to 37 weeks of gestation and then 12 weeks postpartum. Subjects refrained from cigarette and caffeine consumption for 12 hours before each session, and the studies were performed in a quiet temperature-controlled room. Subjects were studied in the supine position, with left uterine displacement maintained during the pregnancy study. Venous tone and response were measured and recorded using the LVDT placed over a vein on the dorsum of the hand as described by Aellig and.
Vascular Sensitivity to PE and ISO During Pregnancy and Postpartum (n=18)

<table>
<thead>
<tr>
<th></th>
<th>Pregnancy (32 to 37 Weeks of Gestation)</th>
<th>Postpartum (12 to 14 Weeks Postpartum)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE ( CD_{50} ), ng/min</td>
<td>2723 (1496, 4955)</td>
<td>433 (270, 690)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>ISO ( ED_{30} ), ng/min</td>
<td>19.7 (10.9, 35.5)</td>
<td>7.7 (4.8, 12.3)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>ISO ( E_{\text{max}} ), %</td>
<td>81 (65, 97)</td>
<td>105 (87, 113)</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

Data are presented as mean (95% CI).

*Pregnancy versus postpartum.

Considered 0% dilatation and baseline vein size before constriction considered 100% (full) dilatation. The ISO log dose-response curves were analyzed by nonlinear regression yielding the half-maximal effect dose (\( ED_{50} \)) and \( E_{\text{max}} \), the maximal (plateau) effect. The log \( ED_{50} \) was used for statistical analysis and expressed as geometric mean (95% CI). The paired \( t \) test was used for comparison of \( ED_{50} \) and \( E_{\text{max}} \) during and after pregnancy.

In addition, 8 healthy women who had not been pregnant in the previous 12 months were studied on 2 occasions during the same phase of their menstrual cycle (4 weeks apart) to confirm the reproducibility of vascular sensitivity measurements obtained in the same individual on different days and to determine if vascular responses differed in women in the postpartum period from those who had not recently been pregnant.

The linear and nonlinear curve fitting and statistical analysis of the dose-response curves was performed using Prism 2.0 for Macintosh, Graphpad Software. Other statistical analysis was performed using Statview 4.5 for Macintosh, Abacus Concepts.

**Results**

Twenty women (14 Hispanic, 3 white, and 3 African-American) with an average age of 28 years (range, 18 to 42 years) were studied. The data from 2 women were not analyzed. One subject did not constrict in response to PE even at the highest dose during pregnancy and did not return for the postpartum study. In a second woman, 50% constriction could not be achieved during pregnancy even at the highest dose we used in this study (9600 ng/min).

The mean PE dose required to achieve 50% constriction in pregnancy was almost 7 times greater than that required postpartum (Table, \( P<0.01 \)). The linear portion of the composite dose-response curve determined for PE during pregnancy and postpartum is illustrated in Figure 1. There was approximately one log unit displacement of the PE dose response to the right during pregnancy (ie, higher dose required in pregnancy), and the \( CD_{50} \) was lower postpartum in all 18 women (Figure 2).

The mean \( ED_{50} \) for ISO during pregnancy was 2.5 times the \( ED_{50} \) postpartum (Table, \( P<0.05 \)), and ISO \( E_{\text{max}} \) was reduced during pregnancy (\( P<0.01 \)). The decreased ISO \( E_{\text{max}} \) during pregnancy reflects the finding that 12 of the 18 subjects did not achieve a 90% return to baseline (prephenylephrine vein size) during pregnancy, whereas only 3 did not do so postpartum. Figure 3 illustrates the mean dose-response curves for ISO during pregnancy and postpartum with a right shift of the curve during pregnancy. The \( ED_{50} \) was lower postpartum in 13 of the 18 women.

The decreased sensitivity during pregnancy was seen in all (18 of 18) women in the \( \alpha \) adrenoceptor response and less consistently (13 of 18) in the \( \beta \) adrenoceptor response (\( P<0.01 \)). An \( \alpha/\beta \) ratio was calculated from the log difference in each subject’s \( \alpha \) versus \( \beta \) decrease in sensitivity in...
pregnancy versus postpartum and just failed to achieve statistical significance ($P=0.065$).

Within the postpartum study group, there was no difference in any of the vascular response parameters between the women who were breastfeeding ($n=8$) and those who were not ($n=10$) (data not shown).

No systemic hemodynamic effects (changes in maternal heart rate, blood pressure, or FHR) were noted in any of the 20 pregnant subjects during the drug infusions. In particular, no woman became tachycardic during the ISO infusion, even at the maximal administered dose (480 ng/min). During the postpartum session, tachycardia (>120 bpm) was recorded at this maximal dose of ISO (480 ng/min) in 5 women, all of whom noted palpitations; heart rate returned uneventfully to baseline values soon after the infusion was interrupted. No changes in blood pressure were noted during the postpartum session in any of the 19 subjects.

In the 8 women studied who had not recently been pregnant, there were no differences between study sessions in the PE CD$_{50}$, 0.51 $\mu$g/min (95% CI, 0.18 to 1.5) at the first session and 0.42 $\mu$g/min (95% CI, 0.16 to 1.1) at the second. ISO effects were also unchanged between sessions. ED$_{50}$ was 15 ng/min (95% CI, 7 to 35) at the first session and 12 ng/min (95% CI, 5 to 28) at the second, and ISO E$_{\max}$ was 94% (95% CI, 80 to 107) at the first session and 93% (95% CI, 78 to 107) at the second. Comparing the second session of the controls to the postpartum session of subjects, vascular response did not differ between the 8 women not recently pregnant (ISO ED$_{50}$ 12 ng/min [95% CI, 5 to 27]; PHE CD$_{50}$ 0.4 $\mu$g/min [95% CI, 0.16 to 1.1]) versus the postpartum subjects (ISO ED$_{50}$ 8 ng/min [95% CI, 5 to 12]; PE CD$_{50}$ 0.4 $\mu$g/min [95% CI, 0.3 to 0.7]).

**Discussion**

We found that $\alpha_1$ adrenoceptor–mediated venoconstriction and $\beta_2$ adrenoceptor–mediated venodilation are blunted during pregnancy, with an $\approx$7-fold decrease in sensitivity to PE and a 2- to 3-fold decreased sensitivity to ISO. The responses to adrenergic agonists during pregnancy have not previously been studied using the LVDT.

Vascular reactivity during normal pregnancy seems to be blunted, but only a few studies have assessed the response to infusions of vasoactive drugs in vivo. An attenuated arterial response to $\alpha_1$ agonist stimulation in late normotensive pregnancy (36 to 41 weeks) compared with early pregnancy (9 to 15 weeks) and to the nonpregnant state (controls) has been demonstrated using venous occlusion plethysmography with a brachial artery infusion of norepinephrine. Overall, the evidence is consistent that angiotensin II vasoconstriction is diminished during pregnancy, with more varied results in studies of norepinephrine-mediated vasoconstriction. In a study using brachial artery infusion and plethysmography, the hemodynamic effects of ritodrine (a $\beta_2$-adrenoceptor agonist) were unaltered by pregnancy or preeclampsia. Thus, pregnancy may diminish vasoconstricting or $\alpha_1$-adrenergic responses to a greater degree than the $\beta_2$-adrenergic vasodilating response. Our finding of a markedly decreased $\alpha_1$ response...
suggests that attenuation of response to this receptor system is an important vasoregulatory mechanism during pregnancy. Our finding of a significantly diminished response to $\alpha_1$-adrenergic stimulation in pregnancy is consistent with results showing an attenuated response to norepinephrine in late pregnancy and conforms to the concept that physiological adaptation to pregnancy requires vasodilation. Our finding of lesser decreases in $\beta$-adrenoceptor responses may partially explain the mixed findings in previous studies examining agents with $\beta$-adrenergic activity.

The blunted response to $\beta$-adrenergic vasodilation in our healthy subjects would seem not to conform to the idea that normal pregnancy enhances vasodilation. However, the shift in the balance of adrenergic tone resulting from a marked decrease in $\alpha$-adrenergic with a smaller decrease in $\beta$-adrenergic sensitivity would produce the vasodilated state characteristic of pregnancy. Several molecular mechanisms could contribute to a decreased $\beta$-adrenergic response during pregnancy. The circulating lymphocyte has been used as an in vivo model for the study of $\beta$-adrenoceptor function, and several investigators have reported that $\beta$-adrenoceptor number or function is decreased in lymphocytes during pregnancy, but others report no significant change compared with the nonpregnant state. Other explanations for $\beta$-adrenoceptor functional changes during pregnancy include alterations of the $\beta$-adrenoceptor $G$ protein coupling or reduced adenyl cyclase particularly at the end of pregnancy. It is likely that some alterations in the coupling between $\beta$-adrenoceptor and adenyl cyclase allow uterine quiescence during pregnancy and that the abrupt decrease of adenyl cyclase at the end of pregnancy contributes to the initiation of labor. cAMP concentrations (basal and evoked by ISO) in lymphocytes are significantly lower at as early as 16 weeks of gestation, with a progressive decline in sensitivity of platelets to agents that act via generation of cAMP during pregnancy, with this effect being maximal at 36 weeks of gestation. The above studies have focused mostly on alterations of the $\beta$-adrenoceptor adenyl cyclase system of the uterus that might trigger or permit labor at term or preterm. However, they provide evidence that mechanisms exist to significantly modify $\beta$-adrenoceptor function in other organs (eg, vasculature) during pregnancy.

Intravascular volume increases by 35% to 50% during pregnancy. This volume expansion presumably maximizes uteroplacental perfusion and protects the fetus during times of moderate maternal dehydration and protects the mother during the obligate blood loss that will occur at delivery. Most pregnant women exhibit a widened pulse pressure produced by a small fall in systolic pressure accompanied by a more significant fall in diastolic pressure. These changes becomes evident during the first trimester, becoming more pronounced during the second trimester, and may diminish at term, with blood pressures occasionally returning to prepregnancy values. Much of the change in cardiovascular parameters occurs by 8 weeks of gestation, suggesting that hormonal or receptor-mediated alterations rather than gross anatomical changes may be the predominant cause. The precise nature of the molecular alterations that cause or allow these hemodynamic changes to occur is unclear. However, the decreased response to adrenergic stimulation in our study cannot be explained by systemic or cardiac reflex effects and does imply alterations at the level of the vascular adrenoceptors or intracellular signaling pathways.

Our findings of altered adrenergic vascular sensitivity in healthy pregnant women may provide insight into the pathogenesis of preeclampsia, where the pregnancy-induced adaptations in vascular tone that should occur in normal pregnancy seem to be impaired, perhaps early in pregnancy before the onset of preeclampsia. The hemodynamic alterations associated with preeclampsia are regulated by several pathways, including the adrenergic system and NO pathway. However, the molecular mechanisms resulting in differences in vascular reactivity in preeclamptic and normal pregnant women remain unclear. It has been shown that $\beta_2$-adrenoceptor density and function differ between healthy women and preeclamptic women. The decrease in $\beta_2$-adrenoceptor number detected during normal pregnancy was reported not to occur in women with pregnancy-induced hypertension. Recently, another study described an increased fraction of receptors in high-affinity state with an unchanged total receptor density in normal pregnancy, whereas preeclampsia seemed to reduce the number of functional $\beta_2$-adrenoceptors attributable to a decreased total receptor number with an unaltered fraction of high-affinity receptors. These findings confirm that the physiological adaptations to normal pregnancy, which include a diminished response to both $\alpha$- and $\beta$-adrenergic agonists, are impaired in preeclampsia.

Studying vascular reactivity in vivo in humans during pregnancy is difficult and ideally requires a technique that is noninvasive, does not activate systemic reflex responses, and results in negligible fetal exposure to drug. The dorsal hand vein/LVDT technique fulfills many of these requirements, allowing direct measurement of changes in vein diameter during infusions of vasoactive drugs, without eliciting clinically significant (and potentially confounding) changes in systemic hemodynamics. The present study describes the successful and safe application of this technique to the study of pregnant women and suggests that it overcomes many of the methodological obstacles that have limited the study of vascular reactivity in pregnancy. The LVDT method should allow the examination of in vivo human vascular response to a variety of agents in preeclampsia and other hypertensive pregnancies.

In summary, using the dorsal hand vein/LVDT technique, we demonstrated markedly decreased $\alpha$ and $\beta$-adrenergic vascular sensitivity during normal pregnancy with the balance shifted toward attenuated vasoconstriction. An impaired ability to attenuate $\alpha$-adrenergic vasoconstrictive responses may be important in the pathogenesis of conditions such as pregnancy-induced hypertension or those associated with decreased uteroplacental blood flow. Based on these results, future studies to examine the balance of adrenergic vascular reactivity in hypertensive pregnancies, the vascular effects of treatments such as magnesium and $\beta$-agonists, and the influence of genetic variants of $\alpha$-adrenoceptors and $\beta$-adrenoceptors on vascular reactivity in pregnancy will be of interest.
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References
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