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Autonomic Circulatory Control during Pregnancy in Humans

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Abstract

Pregnancy is associated with dramatic alterations in maternal hemodynamics, which begin early (i.e., following conception, 4 to 5 weeks of gestation) and are accompanied by changing levels of various pressor hormones and vasoactive metabolites. It has been proposed that these changes occur through autonomic control mechanisms, but the actual role of the autonomic nervous system in pregnancy is poorly understood. New research has shed more light on the links between pregnancy and cardiovascular diseases. Thus, the understanding of the pathophysiology underlying autonomic control of maternal hemodynamics is extremely helpful and particularly important for prevention of cardiovascular complications during pregnancy, and for an improved medical care for all pregnant women and beyond into later life. In this review, we highlight some previous results of hemodynamic adaptation and hormonal effects during pregnancy, changes in vascular endothelial function associated with pregnancy, sympathetic neural control and vascular responsiveness in pregnancy, and baroreflex function during pregnancy in humans. However, whether and how the sympathetic nervous system plays a role in hemodynamic homeostasis during *early* human pregnancy remains completely unknown.

Keywords

pregnancy; vasomotor sympathetic activity; arterial pressure; baroreflexes

Introduction

In humans, normal pregnancy is associated with dramatic changes in hemodynamics, which begin early (i.e., following conception, 4 to 5 weeks of gestation) and are accompanied by changing levels of various pressor hormones and vasoactive metabolites. These changes are detectable by 4 weeks,^{1, 2} and are nearly completed in the first half of pregnancy.^{3–6} It has been proposed that hemodynamic changes during pregnancy occur through autonomic control mechanisms,⁷ but the actual role of the autonomic nervous system in pregnancy is poorly understood. Furthermore, it is completely unknown whether and how the sympathetic nervous system plays a role in hemodynamic homeostasis during *early* pregnancy in healthy women and in women with gestational hypertension or preeclampsia.

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Hemodynamic Adaptation and Hormonal Effects during Pregnancy

Previous studies have suggested that maternal hemodynamic adaptation to pregnancy is most likely triggered by a primary fall in systemic vascular tone.^{4, 6} Cardiac output rises approximately 40% during pregnancy as the result of the fall in systemic vascular resistance and an expansion of blood volume that serve to decrease afterload and increase preload, respectively.⁴ There are several possible explanations for the fall in systemic vascular resistance during pregnancy in humans, which include the development of a new uteroplacental vascular circuit likened to an arteriovenous fistula, the retention of fluids leading to expansion of blood volume, and primary systemic vasodilation (Figure 1).

Creation of the new uteroplacental vascular circuit is not sufficient to explain the systemic vascular resistance fall, since much of the fall occurs outside the uteroplacental circulation.⁸ Furthermore, it was found that women demonstrated hemodynamic changes in the post-ovulatory or the luteal phase of the menstrual cycle qualitatively similar to early pregnancy,² while these changes were exaggerated during ovarian hyper-stimulation,⁹ suggesting that the initial hemodynamic changes of pregnancy may occur early and not require an intact maternal-fetal-placental unit.

Expansion of blood volume occurs as early as 4 weeks in pregnancy and is associated with an activation of the renin-angiotensin-aldosterone system.^{10–13} Products of conception, rather than the fetus, are thought to be a prerequisite for the increase in blood volume.¹⁰ It has been suggested that the stimulus to volume expansion during pregnancy is hormonal. Previous studies using oral estrogen and progesterone in postmenopausal women demonstrated that both hormones activated the renin-angiotensin-aldosterone system.^{14, 15} However, one report showed that progesterone activated while estrogen inhibited this system.¹⁶ Activation of the renin-angiotensin-aldosterone system not only can lead to volume retention but also vasoconstriction, producing an increase in arterial pressure,¹⁷ which may counter peripheral vasodilation in pregnant women. Conversely, Chapman *et al*¹⁰ showed that the hormonal changes associated with pregnancy had a specific renal vasodilating effect, overriding secondary activation of other renal vasoconstricting systems such as the renin-angiotensin-aldosterone system. Thus, arterial pressure decreases in normal pregnancy.

Primary vasodilation is supported by the early onset of the systemic vascular resistance fall, beginning during the luteal phase of the menstrual cycle following conception, and therefore, arterial pressure usually decreases during early pregnancy in humans.¹⁰ These changes precede activation of the renin-angiotensin-aldosterone system and the expansion of blood volume.¹ The mechanism(s) underlying the primary reduction in peripheral vascular resistance in early pregnancy is unclear, but the endothelial release of nitric oxide has been proposed as one major determining factor. Estrogens upregulate nitric oxide synthesis in animals,¹⁸ and therefore, a significant increase in circulating estradiol concentration during early pregnancy¹⁹ could stimulate an increment in nitric oxide synthesis.²⁰ In addition, cardiac output increases very early in pregnancy as a result of increased heart rate and increased stroke volume.³ Increased shear stress secondary to augmented flow in both systemic and resistance arteries may increase nitric oxide release.

Vascular Endothelial Function in Pregnancy

The peripheral arterial vasculature is maintained in a state of active vasodilation by continuous synthesis of endothelium-derived nitric oxide from L-arginine.²¹ An increase in nitric oxide-mediated dilatation in the cardiovascular adaptation to pregnancy was reported in rats.^{22, 23} Although nitric oxide-mediated vasodilation was observed in the hand during healthy human pregnancy,²⁰ whether other vascular beds respond in the same way as the hand remains unknown.

Flow-mediated dilatation, a non-invasive method using high resolution Doppler ultrasound, is an established approach to assess endothelial function and is highly dependent on the capacity of endothelial cells to release nitric oxide.²⁴ Cross-sectional studies in healthy young women showed that flow-mediated dilatation increased in *late* pregnancy,^{25–28} suggesting that basal and stimulated nitric oxide activity is enhanced in normal pregnancy and may contribute to the decrease in peripheral vascular resistance. There is evidence that endothelial dysfunction is involved in the pathophysiology of gestational hypertension or preeclampsia in humans.^{29, 30} An impaired flow-mediated dilatation has been found in preeclampsia.^{31–34} A very recent nested case-control study conducted in Hispanic pregnant women showed that decreased flow-mediated dilatation was present in the second trimester in women who subsequently developed preeclampsia, while this alteration occurred before the onset of clinical symptoms of preeclampsia.³⁵ Germain *et al* proposed that endothelial dysfunction represented a link between preeclampsia and increased cardiovascular disease later in life.³⁶

New research on human pregnancy demonstrated that circulating inhibitors of endothelial function, such as soluble endoglin, circulating soluble fms-like tyrosine kinase 1 (sFlt1), placental growth factor (PlGF), and vascular endothelial growth factor were involved in the pathogenesis of preeclampsia.^{37–41} Levine *et al*³⁷ reported recently that rising circulating levels of soluble endoglin and ratios of sFlt1: PlGF heralded the onset of preeclampsia.³⁷ Venkatesha *et al*³⁸ showed that soluble endoglin impairs binding of transforming growth factor- β_1 to its receptors and downstream signaling including effects on activation of endothelial nitric oxide synthesis and vasodilation. Dysfunctional endothelial cells could also produce altered quantities of vasoactive mediators leading to a tip in the balance towards vasoconstriction.³⁹

However, an important but fundamental issue that must be addressed is how vascular endothelial function changes during normal human pregnancy. Only one longitudinal study was found in healthy women with a very small sample size ($n = 5$) showing that there was a tendency toward a progressive increase in flow-mediated dilatation from early to late pregnancy.²⁵ Thus, longitudinal studies with more subjects are needed to determine the time course of changes in endothelium-dependent vasodilation in normal human pregnancy.

Sympathetic Neural Control and Vascular Responsiveness in Pregnancy

Earlier human studies on vasomotor sympathetic activity during pregnancy have focused only on plasma norepinephrine concentrations, which range from increased to decreased compared with non-pregnant controls.^{10, 42–44} It is well known that plasma norepinephrine is an insensitive measure of vasomotor sympathetic activity, since it can be affected by many factors, such as efferent nerve discharges, synaptic transmitter release, reuptake mechanisms, clearance, regional blood flow, or plasma volume.⁴⁵ In contrast, the microneurographic technique for obtaining direct intraneural recordings of postganglionic efferent nerve activity (Figure 2) allows a precise, quantitative, and reproducible assessment of sympathetic neural vasoconstrictor activity.^{46, 47} Recent studies have shown that baroreflex control of vasomotor sympathetic activity is similar to those of renal and cardiac sympathetic activity under physiological conditions.^{48, 49} With this technique, Greenwood *et al*^{50, 51} found that vasomotor sympathetic activity increased in women with normal pregnancy and was even greater in hypertensive pregnant women during the third trimester of gestation. They thereby concluded that the marked sympathetic hyperactivity during the latter months of normal pregnancy helped to return the arterial pressure to non-pregnant levels, but when the increase in sympathetic nerve activity was excessive, hypertension ensued. This notion was supported by the findings of Schobel *et al*⁵² and Fischer *et al*⁵³ showing that gestational hypertension and preeclampsia was a state of sympathetic overactivity, which normalized after delivery.

Greenwood *et al*⁵¹ followed three normal healthy pregnant women 6 weeks after delivery and found that vasomotor sympathetic activity decreased dramatically compared with that of during the third trimester. Their preliminary data suggest that normal pregnancy may also be associated with an increase in resting vasomotor sympathetic outflow, and pregnancy per se can result in sympathetic activation despite a normal blood pressure. However, these observations need to be confirmed with more healthy pregnant women. Up to now, there have been only five studies published on direct intraneural sympathetic recordings in human pregnancy, and all have been conducted during *the late stages* of pregnancy.^{50–54} Owing to the invasive procedures of the microneurographic technique, it remains a challenging task to assess directly vasomotor sympathetic activity in human pregnancy, particularly during *the early stages* of gestation.

In contrast to the sympathetic activation, peripheral vascular resistance was found to be even lower in normal healthy pregnant women during their late pregnancies compared with non-pregnant women.⁵⁰ This finding suggests that the transduction of sympathetic traffic into vascular resistance is blunted during pregnancy in humans. The mechanisms responsible for such a blunted vascular transduction during pregnancy are unknown. One early study by Meyer *et al*⁵⁵ showed that estrogen replacement attenuated resistance artery adrenergic sensitivity via endothelial vasodilators such as nitric oxide and prostaglandins in female rats. It was also found that estrogen supplementation selectively attenuated vasoconstrictor responses to norepinephrine in perimenopausal women.⁵⁶ These results suggest that estrogen may decrease the transduction of sympathetic traffic into vascular resistance through local mechanisms in humans. However, this notion does not seem to be supported by our preliminary findings that the transduction of sympathetic nerve activity either into total peripheral resistance or into forearm vascular resistance remained the same although circulating levels of estradiol increased markedly from the early to the late stage of pregnancy (Figure 3). It is possible that the effect of estrogen on vascular transduction reaches a plateau within the first trimester of pregnancy, since it was found in postmenopausal women that flow-mediated vasodilation increased by short-term estrogen replacement therapy, while the same increase however, was achieved by the administration of either 1 mg or 2 mg of estradiol.⁵⁷

Baroreflex Function in Pregnancy

Baroreflexes are important mechanisms for the overall regulation of blood pressure in humans.⁵⁸ Results regarding baroreflex control of heart rate during normal pregnancy are quite controversial; increased,^{59, 60} unchanged,^{61–64} or decreased^{65–72} cardiovagal baroreflex sensitivity has been reported. The discrepancies among these studies may be attributable to differences in methodologies implemented for evaluation of the baroreflex and/or different stages of gestation studied. Conversely, results regarding cardiovagal baroreflex function in gestational hypertension and preeclampsia are relatively consistent and an impaired baroreflex function has been reported.^{72–77}

Surprisingly, there is no information available on whether baroreflex control of vasomotor sympathetic activity is altered during normal pregnancy in humans. The sympathetic baroreflex has been well known to play an important role in arterial pressure maintenance in humans.^{78–80} The marked sympathetic activation during the third trimester of gestation found in healthy pregnant women in previous studies led to the proposal that a decrease in baroreceptor-mediated inhibitory restraint on central sympathetic outflow might be one potential explanation.^{50, 51} It seems likely that either changes in hormonal factors or expansion of blood volume associated with normal pregnancy may affect sympathetic baroreflex function. Indeed, Minson *et al*⁸¹ demonstrated that the hormonal fluctuations (i.e., estrogen and progesterone) occurring during the menstrual cycle altered vasomotor sympathetic outflow and sympathetic baroreflex sensitivity in healthy young non-pregnant women. However, whether the hormonal

changes associated with pregnancy have similar effects on sympathetic baroreflex function in healthy pregnant women remains uncertain.

Significance

Very little is known regarding the autonomic control of hemodynamics in normal pregnancy, and there is no information available on vasomotor sympathetic activity during *early* pregnancy in humans. As the maternal hemodynamic changes occur early and are almost completed in the first half of pregnancy, it is critical to know how the autonomic nervous system plays a role in maternal adaptation during the early stage of gestation. New research has shed more light on the links between pregnancy and cardiovascular diseases. For instance, it was found very recently that risk of acute myocardial infarction was around three to four times higher in normal human pregnancy.⁸² Such marked sympathetic activation has been observed in many cardiovascular diseases, such as myocardial infarction,⁸³ congestive heart failure,⁸⁴ and hypertension.⁸⁵ To understand the mechanisms underlying sympathetic neural regulation of arterial pressure in human pregnancy, especially during early pregnancy, will be extremely helpful and particularly important for prevention of cardiovascular complications during pregnancy in humans, and for an improved medical care for all pregnant women and beyond.

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Figure 1.

A schematic overview of possible mechanisms underlying maternal hemodynamic adaptation during normal pregnancy in humans.

Figure 2.

The microneurographic technique showing a direct intraneural efferent nerve recording and integrated muscle sympathetic nerve activity (MSNA) in humans. Increases in MSNA cause norepinephrine (NE) release from the nerve terminal, while NE bonds to α_1 -adrenergic receptors located on the surface of the blood vessels, causing vasoconstriction.

Figure 3.

The transduction of muscle sympathetic nerve activity (MSNA) into total peripheral resistance (TPR) and forearm vascular resistance (FVR), along with circulating levels of estradiol during early and late pregnancy, and after delivery from one healthy young pregnant women. Fu *et al.* Preliminary data.