Published in final edited form as:

Clin Auton Res. 2020 October ; 30(5): 423–431. doi:10.1007/s10286-020-00703-3.

Neural Control of Blood Pressure during Pregnancy in Humans

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Abstract

Purpose—Previous microneurographic studies found that muscle sympathetic nerve activity (MSNA) increased in normotensive pregnant women and was even greater in women with gestational hypertension and preeclampsia during the *third* trimester. It is possible that sympathetic activation during the latter months of normal pregnancy helps return arterial pressure to non-pregnant levels. However, when the increase in sympathetic activity is excessive, hypertension ensues. The key question that must be addressed is whether sympathetic activation develops *early* during pregnancy and remains high throughout gestation, or whether this sympathetic overactivity only occurs at term, providing the substrate for preeclampsia and other pregnancy-associated cardiovascular complications.

Methods—Literature review.

Results—Recent work from our laboratory and others showed that resting MSNA increased in early-pregnancy, further increased in late-pregnancy, and returned to the pre-pregnancy levels shortly after delivery in healthy women. We found that women who exhibited excessive sympathetic activation during the first trimester, before any clinical signs and symptoms appeared, developed gestational hypertension at term. We also found that corin, an atrial natriuretic peptide-converting enzyme, was increased in the maternal circulation, especially during late pregnancy, as a homeostatic response to elevated sympathetic activity.

Conclusion—These findings provide important insight into the neural mechanisms underlying hypertensive disorders during pregnancy. With this knowledge, early prevention or treatment targeted to the appropriate pathophysiology may be initiated, which may reduce maternal and fetal death or morbidity, as well as cardiovascular risks in women later in life.

Keywords

muscle sympathetic nerve activity; blood pressure; hemodynamics; pregnancy

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Competing Interests

There is no conflict of interest to disclose.

Introduction

Pregnancy is associated with significant changes in maternal hemodynamics that begin as early as 4 weeks of gestation prior to the presence of the fetal-placental unit and plateaus at approximately 20 weeks or the second trimester. During the entire course of pregnancy, cardiac output, blood volume, heart rate, and stroke volume increase, and total peripheral resistance decreases [1, 2]. Activation of the renin-angiotensin-aldosterone system increases sodium and water reabsorption from the kidneys, increasing blood volume [2]. Atrial natriuretic peptide secretion by the heart is increased in pregnancy in response to hypervolemia and atrial distension [3]. Atrial natriuretic peptide has diuretic, natriuretic and vasorelaxant effects, which counteract the action of the renin-angiotensin-aldosterone system at multiple levels. Cardiac output increases by up to 45% due to increases in preload (via increased blood volume) and decreases in afterload (via decreased systemic vascular resistance) and increases in heart rate and cardiac contractility [4, 5]. This is accompanied by a decrease in mean arterial pressure that plateaus in the second trimester and returns to pre-pregnancy levels in the third trimester. These hemodynamic adaptations in response to pregnancy return to preconception levels within 6 months after delivery. These alterations are made early in pregnancy to protect both mother and fetus, support the growth of the fetus and prepare the mother for delivery. Sympathetic activation is a normal adaptation in healthy pregnancy and is thought to occur to counteract the decrease in systemic vascular resistance and prevent arterial pressure from decreasing to deleterious levels. However, excessive activation of the sympathetic nervous system during pregnancy has been linked with gestational hypertensive disorders [6–8]. It has been proposed that the cardiovascular changes during pregnancy occur through autonomic control mechanisms, but the actual role of the sympathetic nervous system in normotensive and hypertensive pregnancies remain largely unclear.

This review is based on a presentation that took place at the 2019 American Autonomic Society meeting during a symposium on gender differences in autonomic control of blood pressure and metabolism. It is largely based on the studies conducted over the last decade in the Women's Heart Health Laboratory at the Institute for Exercise and Environmental Medicine and the University of Texas Southwestern Medical Center with reference to studies conducted in other laboratories to provide a summary of autonomic neural control during pregnancy. Sympathetic neural control during normal pregnancy and gestational hypertensive disorders will be reviewed and the influence of race, multi-parity, personal history of preeclampsia and the interaction between the sympathetic nervous system and the natriuretic peptide system during pregnancy will be highlighted.

Timecourse Changes in Sympathetic Neural Control during Normal Pregnancy

Prior to the research performed in our lab, literature on sympathetic neural control during pregnancy demonstrated sympathetic activation during the third trimester of pregnancy in normotensive pregnancies with excessive increases in muscle sympathetic nerve activity (MSNA) in gestational hypertension and preeclampsia [6–8]. It was unclear whether

sympathoexcitation was only apparent in the later stages of pregnancy or if it occurred earlier as these studies were conducted either cross-sectionally in the third trimester with nonpregnant controls or compared late pregnancy to the postpartum period [7–10]. We have since shown that sympathetic activation occurs in the first trimester, as early as 6 weeks into the gestation period [11]. We followed 21 healthy young women before pregnancy (in the mid-luteal phase of the menstrual cycle when both estrogen and progesterone are high), during early (within 8 weeks of gestation) and late pregnancy (between 32 and 36 weeks), and at postpartum (6–10 weeks after delivery); all had normotensive pregnancies [12]. Microneurography was performed during each testing session to directly measure postganglionic efferent sympathetic nerve discharges. Resting MSNA increased from pre-pregnancy to early-pregnancy, further increased during late-pregnancy, and returned to the pre-pregnancy levels shortly after delivery (Fig. 1). Others have also reported sympathetic activation throughout the course of normal pregnancy [13, 14].

The increase in MSNA during pregnancy may be related to the progressive increases in heart rate as it allows for a greater number of cardiac cycles and therefore, a greater chance of MSNA bursts to occur per minute [13]. However, findings from our lab [11, 12], and others [14–16], demonstrate that elevated MSNA is preserved when controlled for heart rate (i.e., when expressed as bursts per 100 heartbeats) in pregnant women when compared with pre-pregnancy and non-pregnant controls. It has also been found that resting MSNA is positively related to volume regulating factors, such as arginine vasopressin in the third trimester of pregnancy but not in non-pregnant controls further supporting the role of the sympathetic nervous system in maintaining homeostasis during pregnancy [17]. Schmidt and colleagues [18] examined whether sympathetic activation during pregnancy was associated with increased central drive by examining the action potential content in integrative bursts of MSNA. Despite a greater incidence of MSNA bursts in late pregnancy, the number of action potential firing within an integrated burst was comparable to non-pregnant controls. It appears that sympathetic activation is a normal adaptation to pregnancy and occurs through the baroreflex to counteract the decrease in systemic vascular resistance and try to restore mean arterial pressure. Consistent with the findings from previous studies [1, 4, 13, 14], we also observed a transient decrease in blood pressure, especially diastolic blood pressure during early pregnancy. The decrease in blood pressure during early pregnancy despite sympathetic activation may be due to profound vasodilation in other vascular beds (e.g., renal, splanchnic, etc.) which overrides the vasoconstrictory effects of MSNA in the skeletal muscle. This is attributed, at least in part, to increased levels of hormones such as estrogen and relaxin which enhance vasodilation during pregnancy [1, 2, 14]. Blood pressure returned to the pre-pregnancy levels during late pregnancy and decreased slightly after delivery (Fig. 2a and 2b). Heart rate increased during late pregnancy and decreased markedly after delivery (Fig. 2c). Recent large scale studies that reassessed blood pressure trajectories during pregnancy have shown no significant changes in blood pressure from early to mid-pregnancy [19, 20]. Preliminary findings from our laboratory reveal similar findings - arterial pressure decreased from pre-pregnancy to early-pregnancy, maintained at this level during mid-pregnancy and returned to pre pregnancy levels in late-pregnancy.

In addition to the resting supine condition, we also examined MSNA responses to upright tilt during pregnancy, as human beings spend approximately two-thirds of the day in the upright

position. In response to upright tilt, we found an increase in MSNA at 30° and a further increase at 60° before pregnancy [11]. During early pregnancy, MSNA was greater in both supine and upright positions compared with pre-pregnancy [11]. However, the magnitude of change in MSNA from supine to upright was the same between these two conditions indicating that early pregnancy does not impact MSNA responses during upright tilt. Contrary to early pregnancy, we found that MSNA responses to 60° upright tilt were blunted during late pregnancy and postpartum (Fig. 3). Despite enhanced MSNA, more women developed presyncope in early pregnancy than in pre-pregnancy (ie, 26% versus 9%, Chi-square $P<0.01$) [11]. The greater incidence of presyncope in early pregnant women may be attributed to impaired baroreflex function in the upright position.

By calculating the slope of the correlation between beat-to-beat diastolic pressure and MSNA during spontaneous breathing, sympathetic baroreflex sensitivity (BRS) can be quantified [21]. Previous case reports have shown sympathetic BRS to be attenuated [14] or enhanced [13] during early pregnancy. In contrast, we found that sympathetic BRS was not significantly different from pre-pregnancy to early pregnancy in the supine position or during a graded upright tilt (Fig. 4). Recent cross-sectional studies have shown that sympathetic BRS is lower in normotensive late pregnant women than age-matched non-pregnant women in the semirecumbent position [15]. Usselman and colleagues [15] reported a blunted sympathetic BRS in late pregnancy when compared with non-pregnant controls. They also report that the slope of the relationship between diastolic pressure and MSNA was shifted rightward towards greater levels of MSNA - there was a greater probability of a burst to occur for any given pressure. The authors suggest this shift in sympathetic BRS indicates a blunting of sympathetic vascular transduction as the operating point of baroreflex is at higher MSNA but similar blood pressure range to non-pregnant controls.

Despite augmented vasomotor sympathetic outflow, pregnancy is associated with decreases in systemic vascular resistance. Indeed, we found that sympathetic vascular transduction, estimated as forearm vascular resistance divided by MSNA was blunted during early pregnancy compared with pre-pregnancy [11]. Others have also shown that sympathetic activation during pregnancy is offset by a dampened vascular transduction both at rest and during a sympathoexcitatory maneuver [14, 16, 22]. The possible mechanisms for the blunted sympathetic vascular transduction during pregnancy may include but are not limited to (1) an increase in circulating levels of estrogen, which has a profound vasorelaxant effect [11]; (2) an increase in nitric oxide release associated with the increase in estrogen, contributing to systemic vascular dilation and a decrease in systemic vascular resistance [23]. Previous animal work has shown increased blood pressure and enhanced vascular reactivity in pregnant rats but not in virgin rats following chronic administration of nitric oxide synthase inhibitor [24]; (3) an increase in receptor sensitivity for other vasodilator compounds such as increased expression of angiotensin type 2 receptors [25]; (4) decreases in α_1 -adrenergic and angiotensin type 1 receptor sensitivity and/or density [25]; (5) an increase in β_2 -adrenergic receptor sensitivity and/or density [26]. Although others have reported a decrease in both α_1 -adrenoreceptor and β_2 -adrenoreceptor sensitivity in dorsal hand vein in pregnant women [27], the greater decrease in sensitivity of α_1 -compared to β_2 adrenoreceptor sensitivity (7 fold vs. 2–3 fold decrease) results in a shift in the balance between these two adrenoreceptors towards vasodilation [27]; and (6) changes in

neurotransmitter kinetics such as release and/or reuptake of norepinephrine within the neurovascular junction; however, this has yet to be directly examined.

Race and Sympathetic Regulation in Pregnancy

Literature on the health-related outcomes during pregnancy suggest apparent racial discrepancies. In the US, between 2011 and 2013, African American women were 3.4 times more likely to die from pregnancy-related complications than Caucasian women [28]. Additionally, pregnancy-related mortality ratios (deaths per 100,000 live births) were 12.7 for Caucasian women, 43.5 for African American women, 11.0 for Hispanic women and 14.4 for women of other races [28]. It has recently been shown that Asian women have a lower incidence of gestational hypertensive disorders when compared with Caucasian or African American women [29]. Furthermore, there are racial disparities in the prevalence of preeclampsia, and the rate of preeclampsia is the lowest in Asian women and highest in African American women [30]. The underlying mechanisms of these racial discrepancies are unclear but may be related, in part, to sympathetic neural control. Studies on the sympathetic nervous system and its role in gestational hypertensive disorders have predominantly been conducted on Caucasian women in the third trimester [6, 7, 9, 10]. Evidence of racial differences in sympathetic neural control in non-pregnant women is limited. Resting MSNA has been shown to be similar between nonpregnant Caucasian and African-American [31], and also between Caucasian and Asian women [32]. However, other reports have demonstrated greater vascular transduction [33] and reactivity to physiological stress [34] in African American men and women when compared with Caucasians. Furthermore, in response to orthostatic stress, African American women were observed to rely more on renal-adrenal system to maintain arterial pressure where Caucasian women rely more on increases in MSNA [35]. Our laboratory was the first to examine the impact of race on sympathetic regulation in pregnancy. We followed a group of healthy young Caucasian and Asian-American women prior to pregnancy, throughout the entire course of gestation, and during post-partum [12]. Asian women were selected when all four grandparents and both parents were of the same racial category. Resting MSNA was significantly lower in Asian women than Caucasian women during pregnancy. Mean arterial pressure was also lower in Asian women during pregnancy, but heart rate was similar between groups. We also found that forearm vascular resistance was lower in Asians than Caucasians during pregnancy and postpartum (Fig. 5a). However, all variables were not different between Asian and Caucasian women prior to pregnancy. Plasma norepinephrine concentration was also lower in Asians during pregnancy (Fig. 5b). On the other hand, direct renin trended higher and aldosterone concentration was higher in Asians than Caucasians during pregnancy (Fig. 5c and 5d). The increase in estradiol levels during pregnancy was greater in Asians but increases in progesterone were similar between Asians and Caucasians. Mean arterial pressure was positively correlated with resting MSNA in Caucasian women but not Asian women whereas mean arterial pressure was positively related to plasma aldosterone levels in Asian women but not Caucasian women. Taken together, these results suggest that Asian women have less sympathetic activation but more upregulated renal-adrenal responses than Caucasian women during normal pregnancy. In addition to Asians and Caucasians, we are following African American and Hispanic women during pregnancy in our current studies to provide more

information on the influence of race on sympathetic neural control in pregnancy and its impact on pregnancy outcomes.

Influence of Multi-parity on Sympathetic Neural Activity during Pregnancy

Evidence suggests that multi-parity (repeated pregnancy) is associated with an increased risk of cardiovascular disease development in women later in life [36, 37]. For instance, women who had two or more pregnancies were at a greater risk of coronary artery disease later in life than those who only birthed one child [38]. Literature on the influence of multi-parity on subsequent pregnancies provides inconsistent findings. Multi-parity has been associated with lower blood pressures during pregnancy and lower risk of gestational hypertension and preeclampsia [39]. Though, others have reported that multi-parity is related to an increased risk of gestational hypertensive disorders in subsequent pregnancies [40]. The underlying mechanisms of cardiovascular risk later in life are unknown but may be attributed in part to altered within-pregnancy sympathetic neural regulation in women with repeated pregnancy. We collaborated with Drs. Craig Steinback and Margie Davenport at the University of Alberta in Canada and studied 10 women in the third trimester with repeated pregnancies [41]. The age between the first and second pregnancy was significantly different, but height, weight, body mass index, and gestational age were similar between the two pregnancies. Resting systolic and diastolic blood pressure did not differ between the two pregnancies. However, there was a trend for heart rate to be greater in the second pregnancy than the first one after adjusting for age ($P=0.06$). This aligns with previous findings where the magnitude of timecourse changes in arterial pressure was similar between nulliparous and multiparous women but increases in cardiac output and decreases in peripheral vascular resistance were significantly greater in multiparous women [42]. Resting MSNA burst frequency was significantly greater during the second than first pregnancy after adjusting for age ($P=0.049$), while sympathetic BRS was not different between these two conditions. These findings suggest greater vagal withdrawal to the heart and increased sympathetic activation to both the heart and skeletal muscle vasculature during the second pregnancy. The mechanisms facilitating increases in MSNA with repeated pregnancy warrant further investigation. Furthermore, how this contributes to increased cardiovascular risk remains unclear. One theory may be that since sympathetic activation increases from one pregnancy to the next, it may predispose women to gestational hypertensive disorders in subsequent pregnancies, which is a risk factor for future cardiovascular disease [41, 43].

History of Preeclampsia and Sympathetic Nerve Activity in Subsequent Pregnancies

Gestational hypertensive disorders affect up to 10% of pregnancies worldwide with preeclampsia as the leading cause of maternal and perinatal morbidity and mortality [44]. A personal history of gestational hypertensive disorders has demonstrated to be a major risk factor for the development of cardiovascular complications in future pregnancies [45]. For instance, women who had preeclampsia during their first pregnancy were found to have a 7 times greater risk of preeclampsia in subsequent pregnancies than women with a history of normal pregnancy [45]. Women with gestational hypertensive disorders, such as

hypertension and preeclampsia, have greater levels of sympathetic activation, with 2 to 3 fold greater resting MSNA when compared with normotensive pregnant women [6, 7, 9, 10]. This sympathetic overactivity may partially explain the elevated peripheral vascular resistance observed in preeclampsia [7, 46]. However, the level of sympathetic overactivation was not different between gestational hypertensive and preeclamptic women [6]. Moreover, sympathetic activation occurs before the presence of preeclampsia in high-risk patients [8]. These findings suggest that sympathetic activation is a precursor to preeclampsia but is not the only determinant in this pathology occurring.

We followed women with and without a history of preeclampsia before pregnancy, during early and late pregnancy, and after delivery. It was found that the rate of hypertension in pregnancy during the study was 8% in women without a personal history of preeclampsia, and was 44% in women who had a previous history of preeclampsia [47]. We also found that formerly preeclamptic women with impaired cardiac function before pregnancy had an increased risk for gestational hypertensive disorders in subsequent pregnancies [47]. To compare the level of sympathetic activation in women with or without a history of preeclampsia, we separated our participants into three groups after delivery; i) low-risk group - women with no personal history of preeclampsia, ii) high-risk normal group - women with a personal history of preeclampsia but had normal pregnancies during the study, and iii) women who developed gestational hypertensive disorders during the study [48]. Throughout early and late pregnancy as well as postpartum, we found that resting MSNA was greater in women who developed gestational hypertensive disorders at term than in high-risk women with normal pregnancies and low-risk women with normal pregnancies during the study [48]. This supports the concept that sympathetic activation is a normal adaptation to pregnancy, but when excessive activation occurs, hypertension ensues. Before and throughout pregnancy and postpartum, mean arterial pressure and heart rate, albeit still within normal ranges, were augmented in women who later developed gestational hypertensive disorders, as well as in high-risk women with normal pregnancies [48].

Interaction between the Sympathetic Nervous and Natriuretic Peptide Systems in Pregnancy

The interaction between the sympathetic nervous system and the natriuretic peptide system could impact hemodynamic homeostasis in health and diseased conditions [49]. Atrial natriuretic peptide has sympathoinhibitory effect in humans [50] and lower levels of atrial natriuretic peptide have been linked to sympathetically active states such as hypertension [51]. Corin is an important enzyme in the natriuretic peptide system that converts pro-atrial natriuretic peptide (ANP) to active ANP. Pro-ANP acts on its receptor - natriuretic peptide receptor A (NPRA), which promotes natriuresis, diuresis, and vasodilation, leading to decreases in blood volume and blood pressure [52]. Corin's influence on blood pressure and salt-water balance makes it a key regulator of cardiovascular and renal function [52]. Corin messenger RNA was first detected in samples from the heart of humans and animals [53]. In addition to the heart, corin expression was also detected in the pregnant uterus, which was proposed to play an important role in vascular remodeling and increases in uteroplacental perfusion [54].

Research suggests that corin is involved in the development of gestational hypertensive disorders [54]. Specifically, it was found that corin messenger RNA and protein levels were lower in the uterus, but plasma corin content was higher in preeclamptic women compared with normal pregnant women at term. Other reports have demonstrated elevated levels of plasma corin in hypertensive pregnancy [55–59] but the role of corin in pregnancy was investigated at different time points, with only one study performed longitudinally [56]. It was unclear what was deemed as normal changes of corin throughout pregnancy and its relation to basal blood pressure and what level of corin was related to the development of gestational hypertensive disorders. We performed a longitudinal study and found that compared with pre-pregnancy, maternal circulating corin content increased slightly during early pregnancy, increased significantly during late pregnancy, and returned to pre-pregnancy levels within 6–10 weeks of postpartum [48]. In women who developed gestational hypertension, the change in blood corin content from early to late pregnancy was greater than those with low-risk normal pregnancies [48]. We also found that changes in corin from early to late pregnancy were related to systolic, diastolic and mean blood pressure in late pregnancy, while MSNA indexes in early pregnancy were related to changes in corin from early to late pregnancy. These results suggest that corin concentration may be increased in the circulation as a homeostatic response to elevated sympathetic activity. Corin plays a unique role in blood pressure regulation throughout normotensive and, especially, hypertensive pregnancy and may represent a promising biomarker for determining women at high risk of adverse pregnancy outcomes [48].

Conclusions

Sympathetic activation occurs early during normal pregnancy, sustains throughout gestation, and returns to pre-pregnancy levels shortly after delivery in healthy women. There are apparent racial discrepancies in the sympathetic neural and renal-adrenal responses during pregnancy in Asian women when compared with Caucasians but there is currently no literature on sympathetic neural control for other racial groups such as African American or Hispanic women during pregnancy. Repeated pregnancies have shown to increase sympathetic activation to both the heart and peripheral vasculature in pregnant women. Women with greater risk of gestational hypertensive disorders have similar sympathetic activity but greater blood pressure and heart rate before, during and after subsequent normal pregnancies compared with low-risk women. However, gestational hypertensive disorders are associated with augmented sympathetic activity in early and late pregnancy, as well as during postpartum. Finally, corin concentration is increased in maternal circulation, as a homeostatic response to elevated sympathetic activity and may represent a biomarker for the detection of adverse pregnancy outcomes, especially those with a high risk of gestational hypertensive disorders.

Acknowledgments

This brief review article was supported, in part, by the National Institutes of Health grants K23 (HL075283), R21 (HL088184) and R01 (HL142605), the American Heart Association Grant-in-Aid grant award (13GRNT16990064), and the Harry S. Moss Heart Trust.

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Fig. 1.

Time-course changes in resting MSNA during normotensive pregnancy in 21 healthy women. Sympathetic activity increased during early pregnancy, further increased during late pregnancy, and returned to prepregnancy levels 6–10 weeks after delivery. Values are means $\pm$ SEM. * Significant difference vs. pre-pregnancy at $P < 0.05$. MSNA, muscle sympathetic nerve activity. Adapted from Okada et al., 2015

Fig. 2.

Time-course changes in a) systolic blood pressure, b) diastolic blood pressure and c) heart rate at rest in normal pregnancy. Values are means $\pm$ SEM. * Significant difference vs. pre-pregnancy at $P < 0.05$. Adapted from Okada et al., 2015

Fig. 3. MSNA responses to upright tilt in women before, during and after normotensive pregnancy. Values are mean $\pm$ SEM * Significant difference vs. pre and post-pregnancy at $P < 0.05$ MSNA, muscle sympathetic nerve activity (manuscript in preparation)

Fig. 4. Sympathetic baroreflex sensitivity during pre and early pregnancy in healthy women in the supine position and during 30-degree and 60-degree head-up tilt. Values are means $\pm$ SD (manuscript in preparation)

Fig. 5. Changes in a) limb (forearm) vascular resistance, b) plasma norepinephrine concentration, c) direct renin concentration and d) aldosterone concentration during normal pregnancy in Caucasian and Asian women. Values are means $\pm$ SEM. * Significant difference vs. Caucasian women at $P < 0.05$. Adapted from Okada et al., 2015