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ROLE OF CORIN IN BLOOD PRESSURE REGULATION IN NORMOTENSIVE AND HYPERTENSIVE PREGNANCY: A PROSPECTIVE STUDY

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Abstract

Corin (an atrial natriuretic peptide converting enzyme) represents a potential biomarker for gestational hypertensive disorders; yet, its role in blood pressure regulation throughout pregnancy remains unclear. We investigated the time-course of change in blood corin content in relation to blood pressure and sympathetic nerve activity throughout pregnancy. Forty-four women (29±0.9 yrs) participated. Following-term, 23 had 'low-risk' (no personal history of gestational hypertensive disorders) normal pregnancies, 13 had 'high-risk' (personal history of gestational hypertensive disorders) normal pregnancies, and eight developed gestational hypertension. Blood pressure, heart rate, muscle sympathetic nerve activity, and serum corin were measured prior-to pregnancy, during early- (4-8 wks) and late-pregnancy (32-36 wks), and post-partum (6-10 wks). Overall, compared to pre-pregnancy, corin remained unchanged during early-pregnancy, increased markedly during late-pregnancy (P<0.001), and returned to pre-pregnancy levels post-partum. In women who developed gestational hypertension, the change in corin from early- to late-pregnancy was greater than those with 'low-risk' normal pregnancies (Δ971±134 vs. Δ486±79 pg/mL; P<0.05). Throughout pregnancy, blood pressure and muscle sympathetic nerve activity were augmented in women with gestational hypertension (all P<0.05). Finally, changes in corin from early- to late-pregnancy were related to all indices of blood pressure (R=0.454-0.551; all P<0.01) in late-pregnancy, whereas burst frequency, burst incidence, and total muscle sympathetic nerve activity (R=0.576-0.614; all P<0.001) in early-pregnancy were related to changes in corin from early- to late-pregnancy. Corin plays a unique role in blood pressure regulation throughout

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CONFLICT(S) OF INTEREST/DISCLOSURE(S)

None.

normotensive and especially hypertensive pregnancy, and may represent a promising biomarker for determining women at high-risk of adverse pregnancy outcome.

Keywords

Gestational hypertension; Corin; Pregnancy; Blood pressure; Muscle sympathetic nerve activity

INTRODUCTION

Pregnancy-induced hypertensive disorders (i.e., gestational hypertension and pre-eclampsia), which occur in approximately 10% of all pregnancies[1,2], represent a major risk factor for maternal-fetal morbidity and mortality worldwide. Rather alarmingly, women with gestational hypertensive disorders have a higher risk of disease reoccurrence in subsequent pregnancies[3], and furthermore, remain at an elevated risk of cardiovascular disease development in later life, including hypertension, ischemic heart disease, and stroke[4,5]. However, the exact mechanisms and etiology of gestational hypertensive disorders remain elusive, owing largely to the heterogeneous and multi-factorial nature of the disease. As such, this hinders early recognition and accurate diagnosis, and ultimately, effective preventative strategies and management of patients. Therefore, the study of potential evidence-based, pre-clinical biomarkers for the early prediction of risk for hypertensive pregnancy represents a critical endeavor towards the successful diagnosis, management, and prevention of deleterious maternal-fetal outcome.

Corin is a transmembrane serine protease predominantly located in the heart, where it converts atrial natriuretic peptide (ANP) from its precursor peptide (i.e., pro-ANP) to its biologically active form, thereby stimulating natriuresis, diuresis, and vasodilation[6]. Therefore, corin represents a key regulator of cardiovascular and renal function through its influence on blood pressure (BP) and salt-water balance, respectively[6]. In recent years, corin has gathered much attention as a promising biomarker for cardiovascular disease[7], given its association with risk and outcome in many cardiac-related disorders (i.e., hypertension, heart failure, myocardial infarction, stroke)[8–14]. Interestingly, corin has also been found in the pregnant uterus, where it plays an important role in promoting trophoblast invasion and spiral artery remodeling to ensure adequate uteroplacental perfusion[15]. Recently, corin has been identified as a potential contributor to the pathogenesis of pre-eclampsia and hypertensive pregnancy; specifically, uterine *Corin* messenger RNA and protein levels were lower in women with hypertensive pregnancies versus those with normotensive pregnancies[15]. However, somewhat serendipitously, Cui *et al.*[15] discovered that blood corin levels were actually higher in pre-eclamptic women than in those with normal pregnancies. Indeed, a small handful of studies (but not all) have since demonstrated elevated blood corin in hypertensive pregnancy[16–20], yet values were measured at various, inconsistent times during pregnancy and only one was longitudinal in nature[16]. As such, there is limited data on the time-course of change in blood (plasma or serum) corin levels throughout pregnancy and its association with resting BP and its regulatory mechanisms (i.e., sympathetic nerve activity). Therefore, the role played by corin in neuro-cardiovascular control throughout

pregnancy in humans, as well as the potential of corin as a biomarker of gestational hypertensive disorders, remains to be determined.

Therefore, the purpose of the current study was to investigate, in a prospective manner, the time-course of change in maternal blood corin content in relation to resting BP and sympathetic nerve activity throughout pregnancy in women. Specifically, we tested the hypothesis that greater increases in corin content throughout pregnancy would be associated with greater resting BP in late-pregnancy.

METHODS

The authors declare that all supporting data are available within the article.

Participants

Forty-four women who were planning to become pregnant or were within the first eight-weeks of pregnancy participated in the current investigation after providing informed written consent. Participants were non-smokers and free of overt disease. Exclusion criteria included chronic hypertension, recreational drug use or hormonal contraceptives within the previous six-months, hormonal fertility treatment or supplement use, and/or those women with irregular menstrual cycles. All experimental protocols were approved by the Institutional Review Boards at the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas.

All women had singleton, full-term pregnancies. Following term, participants were divided into three groups: 1) those women with ‘low-risk’ (i.e., no personal history of hypertensive pregnancy) normal pregnancies (LR-NP; n=23); 2) those women with ‘high-risk’ (i.e., personal history of hypertensive pregnancy), yet normal pregnancies currently (HR-NP; n=13); and 3) those women who developed gestational hypertensive disorder following their late-pregnancy testing (GHD; n=8)[21]. Of the eight women who developed gestational hypertension, six had a history of hypertensive pregnancy. Within the HR-NP group, eight women had a personal history of gestational hypertension, three had a personal history of pre-eclampsia, one had a personal history of eclampsia, and one had a personal history of HELLP syndrome (a variant of pre-eclampsia characterized by hemolysis, elevated liver enzymes, and low platelet count). Data on pregnancy outcomes were obtained from the hospital maternity records of the women, and diagnoses were made based on the criteria of the American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy[22]. Specifically, gestational hypertension was defined as de novo hypertension (i.e., systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg) at ≥20 weeks of gestation in the absence of proteinuria or new signs of end-organ dysfunction. All eight women who developed gestational hypertension during their pregnancies did so following their late-pregnancy testing visit (see below). None of the women in the present study developed pre-eclampsia. ‘Normal’ pregnancy was defined as those with the absence of gestational hypertensive disorders or other pregnancy-related morbidities (i.e., gestational diabetes).

Study Design and Protocol

Women were tested prior-to pregnancy (mid-luteal phase; n=25), during early- (4-8 wks gestation; n=44) and late- (32-36 wks gestation; n=44) pregnancy, and post-partum (6-10 wks post-delivery; n=43). Prior to each testing day, participants adhered to a two day isocaloric constant diet consisting of 150 mEq sodium, 100 mEq potassium, and 1000 mg calcium, while water intake was *ad libitum*. Experiments were performed ≥2 hours following a light breakfast and participants abstained from caffeine and alcohol for ≥48 hours and strenuous exercise for ≥24 hours prior to study participation. Studies were conducted in a quiet, environmentally-controlled laboratory with an ambient temperature of approximately 25°C. All repeat testing was conducted at the same time of day. Pregnancy was confirmed each testing day by the measurement of beta-human chorionic gonadotropin (β-hCG) level.

Participants were studied in the resting supine (rotated ~15° into the left lateral) position. An intravenous catheter was inserted into the antecubital vein of the left arm for blood samples. Following at least 30-minutes of supine rest, a blood sample was taken for the assessment of corin content, followed by resting BP and heart rate (HR) measures. Finally, at least 10-minutes after a satisfactory nerve recording site had been found, baseline muscle sympathetic nerve activity (MSNA) was measured for 6-minutes during spontaneous breathing.

Experimental Measures and Analysis

Hemodynamics.—HR was determined from lead II of the ECG. Resting BP was measured following at least a 30-minute rest via electrosphygmomanometry (SunTech Medical Instruments Inc., Raleigh, NC), with a microphone placed over the brachial artery to detect Korotkoff sounds[23]. Mean arterial BP was calculated as [(systolic BP − diastolic BP)/3 + diastolic BP]. The average of three BP measurements were used in the final analysis.

Muscle Sympathetic Nerve Activity.—Sympathetic neural recordings were obtained in the right peroneal nerve by microneurography, using standard procedures as outlined originally by Hagbarth and Vallbo[24] and used frequently in our hands[25–27] (662C-3; Bioengineering of University of Iowa, Iowa City, IA). The level of integrated MSNA was quantified using burst frequency (bursts/min) and burst incidence (bursts/100 heartbeats). Furthermore, burst amplitude (normalized within each individual to the largest burst, which was assigned a value of 100 arbitrary units) was determined for the calculation of total MSNA (product of burst frequency and normalized burst amplitude).

Corin.—Maternal corin content was measured via enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN)[28] by a trained investigator blinded to patient data and pregnancy outcome. In brief, microtiter plates were coated with an anti-corin antibody. Next, serum samples or recombinant human corin protein standards were added and incubated at room temperature for two-hours. The plates were washed five times with a wash buffer, and a biotinylated anti-human corin antibody was added and incubated for another two hours. After five more washes, peroxidase-conjugated streptavidin was added

and incubated at room temperature for an additional 30-minutes. The reaction was visualized by adding a horseradish peroxidase substrate (3,3′,5,5′-tetramethylbenzidine; TMB) and the optical density was monitored with a spectrometer at a wavelength of 450 nm. We performed triplicate sample measurements and normalized them by first subtracting 550 nm absorbance values and then the average absorbance of blank wells. The within-individual typical error, expressed as coefficient of variation, for corin measurement was 5.46% and the correlation coefficient between the measurements was R=0.998.

Statistical Analysis

To determine sample size, we used previously published data on the mean difference and SD of maternal corin content (our primary variable of interest) between women with gestational hypertensive disorders and women with normotensive pregnancies[17]. From this work, we anticipated the smallest meaningful difference and SD in corin content to be 550±450 pg/mL. Based on an assigned α of 0.05 and power of 0.80, an estimate of 42 participants in total was deemed sufficient.

One-way repeated measures ANOVA assessed the effect of pregnancy (pre- to early- to late- to post-) on maternal corin content in all participants. The delta change in corin levels from early- to late-pregnancy between groups was assessed using one-way ANOVA. The effect of group and pregnancy on all neural-cardiovascular variables was assessed with a repeated measures analysis using linear mixed models. In addition to the overall average effect, the slope and intercept were allowed to vary from participant to participant (random effect). Specifically, this model provides a more robust analysis of longitudinal data sets through its ability to accommodate missing data points and model non-linear, individual characteristics[29]. Bonferroni-corrected post hoc procedures were used for all analyses, when applicable. Linear regression analyses were used to determine specific relationships between variables of interest. Statistical significance was set at $P<0.05$ and values are presented as mean ± SEM. All statistical analyses were performed using SPSS Statistics (Version 23, Chicago, IL).

RESULTS

Participant characteristics are shown in Table 1. Specifically, there were no differences in age or height between groups (both $P>0.05$), whereas weight was greater in GHD versus LR-NP and HR-NP throughout pregnancy (all $P<0.05$). Weight increased during early- and late-pregnancy (both $P<0.001$ *vs. pre-*); however, the magnitude of weight gain was not different between groups ($P>0.05$).

Compared to pre-pregnancy, corin levels remained unchanged during early-pregnancy, increased markedly during late-pregnancy ($P<0.001$), and returned to pre-pregnancy levels following delivery (Figure 1). In women who developed GHD during their pregnancies, the change in corin levels from early- to late-pregnancy was greater than in those with LR-NP (Δ971±134 vs. Δ486±79 pg/mL; $P<0.05$; Figure 1). Yet, no differences existed in the change in corin levels from early- to late-pregnancy between HR-NP (Δ799±105 pg/mL) and both LR-NP and GHD groups (both $P>0.05$).

Figure 2 displays the changes in resting BP and HR throughout pregnancy. Prior-to pregnancy, systolic BP was not different between groups (all $P>0.05$), whereas diastolic BP and mean arterial BP were greater in GHD versus LR-NP (both $P<0.05$). In all groups, systolic and mean arterial BP increased from early- to late-pregnancy (all $P<0.05$ *vs. early-*) and returned to pre-pregnancy levels following delivery (all $P>0.05$ *vs. pre-*). Conversely, diastolic BP was unchanged throughout pregnancy in LR-NP and HR-NP women (all $P>0.05$). In GHD, diastolic BP decreased during early-pregnancy ($P<0.05$ *vs. pre-*), increased from early- to late-pregnancy ($P<0.05$ *vs. early-*), and remained at pre-pregnancy levels post-partum ($P>0.05$ *vs. pre-*). In women who developed GHD, systolic BP was greater than LR-NP throughout early and late-pregnancy and post-partum, whereas diastolic BP and mean arterial BP were elevated at late- and post-pregnancy (all $P<0.05$). Furthermore, following delivery, HR-NP had greater diastolic BP and mean arterial BP as compared to LR-NP (both $P<0.05$). In all groups, resting HR increased during late-pregnancy (all $P<0.05$ vs. *pre-*). Following delivery, HR was decreased below pre-pregnancy levels in LR-NP and HR-NP (both $P<0.05$ vs. *pre-*), but was not different in GHD ($P>0.05$ *vs. pre-*). Throughout pregnancy, both HR-NP and GHD groups had greater resting HR than LR-NP (all $P<0.05$).

Figure 3 displays the changes in MSNA throughout pregnancy. Prior-to pregnancy, all indices of MSNA were similar between groups (all $P>0.05$). Burst frequency, burst incidence, and total MSNA were increased during late-pregnancy (all $P<0.05$ *vs. pre-*), yet returned to pre-pregnancy levels post-partum (all $P>0.05$ *vs. pre-*). Throughout early- and late-pregnancy, as well as post-partum, all indices of MSNA were greater in women with GHD than in HR-NP and LR-NP groups (all $P<0.05$).

As shown in Figure 4, the change in corin from early- to late-pregnancy was related significantly to systolic BP (R=0.513; $P<0.001$), diastolic BP (R=0.454; $P<0.01$), and mean arterial BP (R=0.551; $P<0.001$) in late-pregnancy. Furthermore, the change in corin from early- to late-pregnancy was related moderately to burst frequency (R=0.349; $P<0.05$), burst incidence (R=0.338; $P<0.05$), and total MSNA (R=0.393; $P<0.01$) in late-pregnancy. However, as shown in Figure 5, burst frequency (R=0.614; $P<0.001$), burst incidence (R=0.576; $P<0.001$), and total MSNA (R=0.606; $P<0.001$) in early-pregnancy were related strongly to changes in corin from early- to late-pregnancy.

DISCUSSION

To our knowledge, this is the first longitudinal study to demonstrate that changes in maternal corin content from early- to late-pregnancy are associated directly with resting BP in late-pregnancy and levels of sympathetic nerve activity in early- and late-pregnancy.

Furthermore, women who develop gestational hypertension display greater increases in corin content during pregnancy as compared to their normotensive counterparts, in addition to elevated resting BP and exaggerated sympathetic nerve activity. Our results suggest that corin plays a unique role in BP regulation throughout normotensive and especially hypertensive pregnancy, and furthermore, may represent a novel biomarker for the early recognition of those women at-risk for gestational hypertension development.

Corin and Blood Pressure Regulation in Pregnancy

Corin plays an important role in cardiovascular control through its regulation of blood volume and BP[6]. Interestingly, corin has been shown to be markedly upregulated in the decidua of the pregnant uterus[15], but is not detected in the non-pregnant uterus[30], suggesting a role as a local adaptive mechanism to ensure adequate hemodynamic homeostasis in early-pregnancy. Indeed, as demonstrated by Cui *et al.*[15], corin expression in the uterus is essential to the development of an adequate uteroplacental vascular circuit through its involvement in spiral artery remodeling. In this sense, corin appears to be involved in the pathogenesis of hypertensive pregnancy. Specifically, when uterine corin levels are low, pre-eclampsia and gestational hypertension ensue[15]. However, somewhat paradoxically, a small but growing body of literature demonstrates that corin levels in the blood are elevated in hypertensive pregnancies[15–20]. Our present findings support this conjecture. Therefore, it appears that corin represents a key regulatory mechanism of arterial BP control throughout pregnancy in humans, and furthermore, may have a unique involvement in the etiology of gestational hypertension.

Furthermore, we extend current knowledge on the relationship between corin and BP control during pregnancy to show for the first time in a prospective manner, that changes in corin content from early- to late-pregnancy are related positively to levels of resting BP in late-pregnancy. Previously, Liu *et al.*[18] investigated plasma corin levels during mid-pregnancy (16-20 wks gestation) in patients who subsequently developed hypertensive pregnancies versus normal pregnant controls. Specifically, women were categorized into quartiles based on corin content, and when compared to the lowest corin quartile, those in the highest quartile demonstrated significantly elevated risk for hypertensive pregnancy. Similarly, Miyazaki *et al.*[19] compared blood samples taken at delivery in women with and without pre-eclampsia, and not only were plasma corin levels higher in pre-eclamptic patients, its concentrations were correlated positively with resting BP. Most recently, Gu *et al.*[20] demonstrated greater plasma corin at late-pregnancy in women with mild and severe pre-eclampsia than in normotensive women. While these findings suggest an important role for corin in human pregnancy, the cross-sectional nature of these studies (and varying time-points in which corin content was measured) prevent conclusions about the time-course or ‘causal’ relationship between maternal corin content and resting BP. In turn, this precludes judgement as to the potential efficacy of corin as a biomarker of gestational hypertensive disorders. In the only other longitudinal study, Khalil *et al.*[16] found no differences in plasma corin levels at mid-pregnancy between women with gestational hypertension or pre-eclampsia at term and normotensive controls (was lower in pre-term pre-eclampsia), yet levels in all groups increased rapidly as pregnancy progressed. Therefore, in line with our current findings, it appears that the (magnitude of) change in plasma or serum corin throughout pregnancy exerts greater influence on late-pregnancy BP and subsequent pregnancy outcome. Indeed, we demonstrate that women who develop gestational hypertension experience the greatest increases in corin content during pregnancy, while a greater change in early-to-late maternal corin is associated significantly with elevated late-pregnancy BP ($R=0.551$; $P<0.001$ for mean arterial BP). As such, the current study highlights the promising potential for corin to be used as a pre-clinical biomarker for determining women at-risk for hypertensive pregnancy.

Sympathetic Nerve Activity in Hypertensive Pregnancy

In the present study, women who developed gestational hypertension displayed markedly elevated sympathetic nerve activity in early- and late-pregnancy. Furthermore, sympathetic nerve activity in early-pregnancy was related strongly to the change in corin levels throughout pregnancy, which was ultimately related to arterial BP in late-pregnancy. Certainly, pregnancy is associated with dramatic changes in maternal hemodynamics, most notably highlighted by a rise in cardiac output and a fall in systemic vascular resistance[31,32]. Both cross-sectional[33–35] and longitudinal[25,26,36] studies have demonstrated elevated sympathetic nerve activity (in the range of 50% to 150%) throughout 'normal' pregnancy. It is thought that this sympathetic hyperactivity helps to counteract the significant fall in systemic vascular resistance and keep resting BP at pre-pregnancy levels. However, when excessive sympathetic activation occurs, gestational hypertensive disorders likely manifest[37–40]. Our present findings support this view. Specifically, all indices of MSNA were augmented in early- and late-pregnancy in the GHD group. It is perhaps likely then, that maternal corin content increased to a greater extent in these women as an adaptive reaction to sympathetic hyperactivity and oncoming high BP. Indeed, ANP exerts sympathoinhibitory effects in humans[41]. Furthermore, it is worth noting that MSNA was not (statistically) increased during early-pregnancy presently, which differs from our previous work[25,26]. While the reason for this discrepancy is unclear, it may be due to the robustness and more conservative nature of the linear mixed model design used in the current analysis, versus paired[26] and unpaired[25] t-test comparisons of the pre-to-early response used previously. Specifically, of the 25 women with pre- and early-pregnancy MSNA data in our current study, 75% experienced an increase in MSNA burst frequency in early-pregnancy (15±2 to 19±2 bursts/min for all 25 women; P=0.048 using paired t-test).

Potential Mechanisms for Corin Response during Pregnancy

Our results provide novel evidence with respect to the association between the magnitude of corin increase throughout pregnancy and elevated resting BP and risk of GHD development. Although beyond the scope of the current investigation, the potential mechanisms mediating the increase in maternal corin content during pregnancy warrants some discussion. As mentioned, pre-eclamptic and hypertensive pregnancies are characterized by low uterine *Corin* messenger RNA and protein levels and impaired spiral artery remodeling in early-pregnancy[15]. Therefore, as it relates to our present findings, perhaps those women destined for higher BP in late-pregnancy (and GHD development) display greater increases in blood corin content (probably derived from the heart) during pregnancy as a compensatory response to decreased corin expression in uterine tissue. Additionally, corin concentration may be elevated in the circulation as a homeostatic response to elevated sympathetic nerve activity and increasing arterial BP during pregnancy (i.e., in an attempt to rescue high or increasing BP levels). Inferring from our own data, both the change in mean arterial BP from early- to late-pregnancy (R=0.564; P<0.001; data not reported) and early-pregnancy MSNA burst frequency (R=0.614; P<0.001) were related directly to the increase in corin content throughout pregnancy. Certainly, elevated blood corin levels have been found in chronic hypertension[14]. However, Miyazaki *et al.*[19] reported elevated corin even in normotensive pregnancy complicated with fetal growth restriction, suggesting that other factors are also in play. Even so, this begs the question as to why BP is not lowered in response to elevated

corin in late-pregnancy. Recently, it was found that while plasma corin was elevated in mild and severe pre-eclampsia, natriuretic peptide receptor (NPR)-A expression was downregulated and NPR-C expression was upregulated, thereby inhibiting the vasorelaxant effects of ANP and increasing ANP clearance and degradation in these patients, respectively [20]. Certainly, these unresolved matters require future investigation.

Study Limitations

First, the number of patients with GHD is relatively small and no women developed pre-eclampsia. However, this limitation is difficult to avoid given the logistical difficulties in performing longitudinal studies in pregnant women and the lack of control in determining pregnancy outcome. Nevertheless, to our knowledge, this is the only prospective study to examine neuro-cardiovascular control throughout pregnancy in women with GHD. Second, weight was greater in women with GHD prior-to and throughout pregnancy (although weight gain did not differ) and corin levels have been shown to be moderately elevated in obese individuals[42]. Yet, our data suggests that corin levels were not related to weight before or during pregnancy. Third, there were differences in racial distribution between groups and the effect of race on corin in pregnancy is unknown. Previously, Khalil *et al.*[16] found lower corin levels in women of Afro-Carribean origin as compared to Caucasian women. Although we studied a limited number of Asians (n=8), African Americans (n=5), and Hispanics (n=5), as compared to Caucasian women (n=26), there did not appear to be any effect of race on maternal corin content. Finally, we did not measure levels of circulating ANP or pro-ANP in our current cohort, yet previous investigations demonstrate similarly elevated plasma levels of ANP and pro-ANP in women with gestational hypertension[6].

Perspectives—Gestational hypertensive disorders are associated with a dramatic increase in risk of adverse maternal-fetal outcome. Certainly, hypertensive pregnancies are a leading cause of maternal-fetal morbidity and mortality acutely; yet, their presence also infers increased risk of future cardiovascular disease development[4,5]. Furthermore, pre-eclampsia is now recognized as an independent risk factor for cardiovascular disease mortality[43]. Currently, management and/or treatment strategies remain limited, owing largely to the multi-factorial nature of the disease. Fundamentally, gestational hypertensive disorders reflect an inherent failure in properly regulating arterial BP homeostasis throughout pregnancy. Our present findings demonstrating the unique involvement of corin in neuro-circulatory control throughout pregnancy offers an exciting new take on an enigmatic disease. Specifically, we show for the first time, that the change in corin content from early- to late-pregnancy is related directly to resting BP levels in late-pregnancy, suggesting that maternal corin content may represent a novel target in the ongoing investigation of useful biomarkers for determining women at high-risk of adverse pregnancy outcome.

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NOVELTY AND SIGNIFICANCE

What is New?

- This is the first longitudinal study to demonstrate that changes in maternal corin content from early- to late-pregnancy are related directly to arterial blood pressure in late-pregnancy and levels of sympathetic nerve activity in early- and late-pregnancy.
- Women who develop gestational hypertension display greater increases in corin content as compared to normal pregnancy, in addition to elevated resting blood pressure and exaggerated sympathetic nerve activity.

What is Relevant?

- Gestational hypertensive disorders are associated with a dramatic increase in risk of adverse maternal-fetal outcome. Our results suggest that corin plays a unique role in blood pressure regulation throughout normotensive and especially hypertensive pregnancy, and furthermore, may represent a promising biomarker for hypertensive pregnancy.

Summary

- We show for the first time here, that the change in corin content throughout pregnancy is related directly to blood pressure levels in late-pregnancy, suggesting that maternal corin content may represent a useful biomarker for the determination of those women at high-risk of adverse pregnancy outcome.

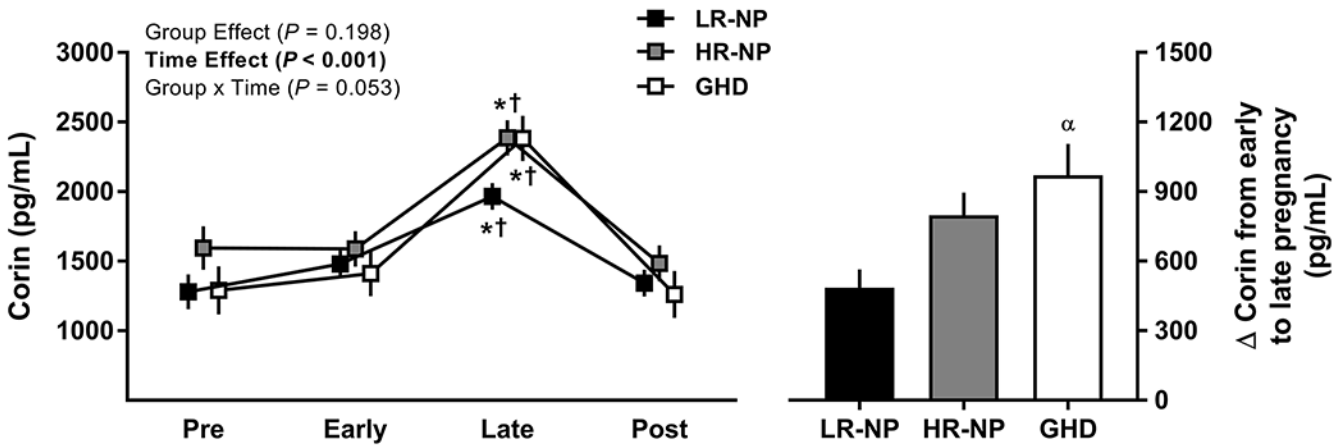

Figure 1.

Maternal corin content at pre-, early-, late-, and post-pregnancy (left panel) and the change in corin from early- to late-pregnancy in 'low-risk' normal pregnancy (LR-NP), 'high-risk' normal pregnancy (HR-NP), and women who developed gestational hypertension (GHD; right panel). *Significantly different from pre-pregnancy, $P<0.001$. †Significantly different from early-pregnancy, $P<0.001$. αSignificantly different than LR-NP, $P<0.05$.

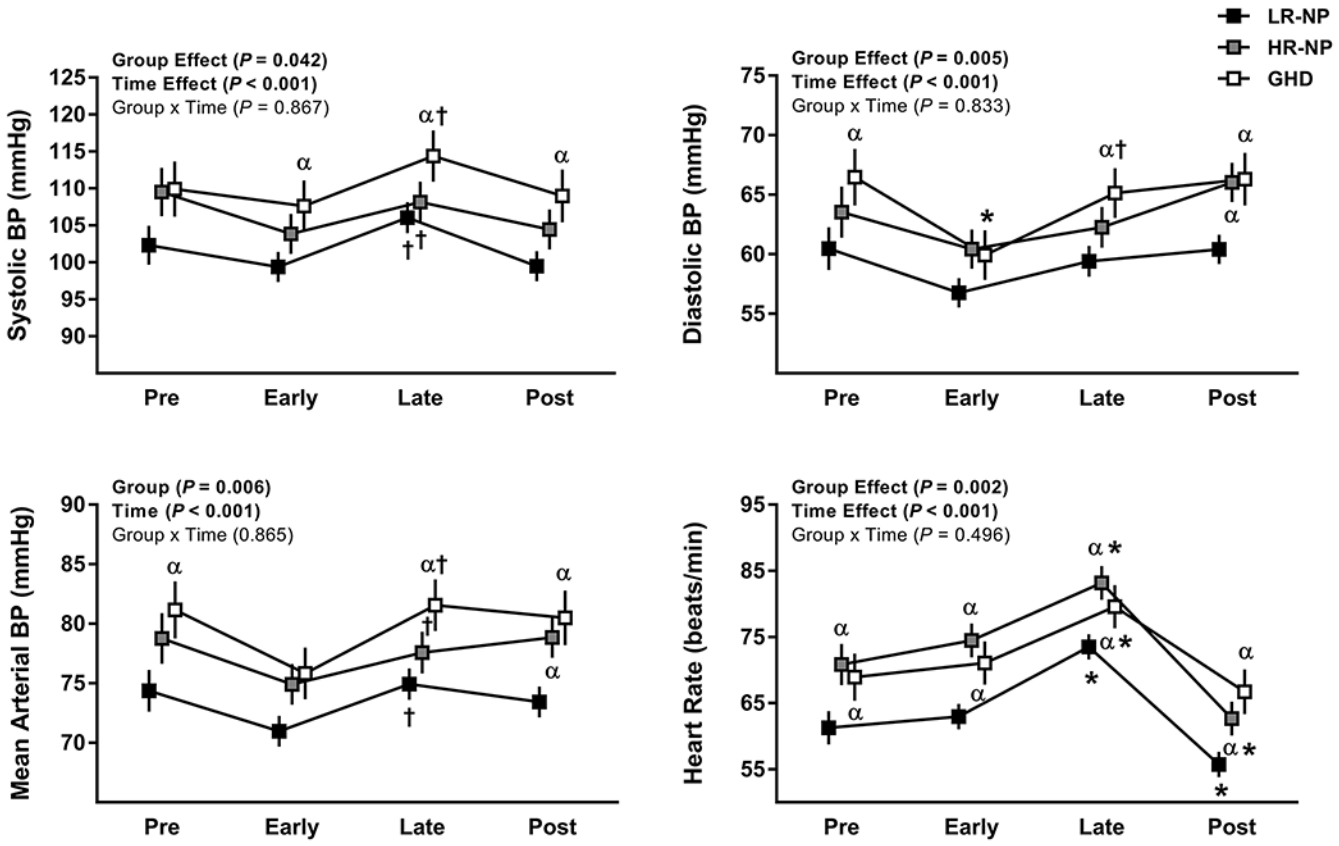

Figure 2.

Resting blood pressure (BP) and heart rate at pre-, early-, late-, and post-pregnancy in 'low-risk' normal pregnancy (LR-NP), 'high-risk' normal pregnancy (HR-NP), and women who developed gestational hypertension (GHD). *Significantly different from pre-pregnancy, $P<0.05$. †Significantly different from early-pregnancy, $P<0.05$. αSignificantly different than LR-NP, $P<0.05$.

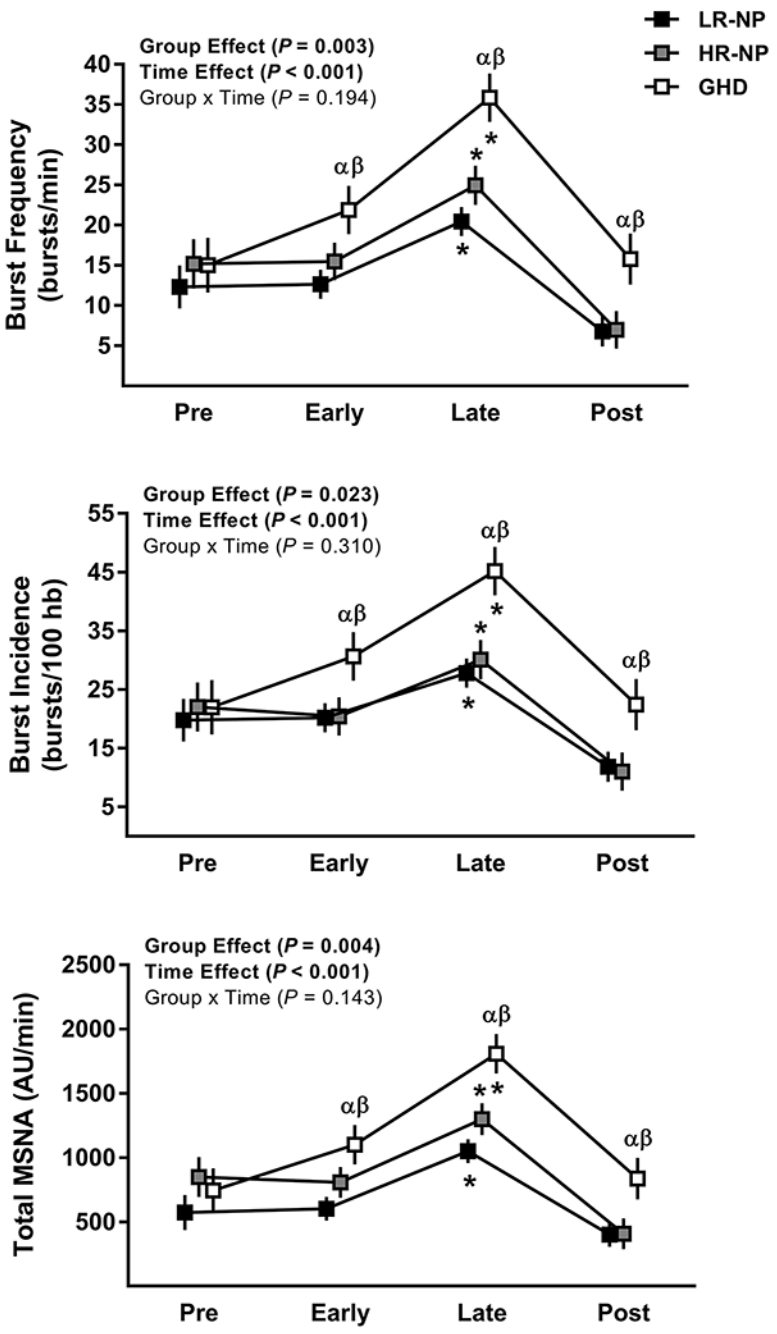

Figure 3.

Muscle sympathetic nerve activity (MSNA) at pre-, early-, late-, and post-pregnancy in 'low-risk' normal pregnancy (LR-NP), 'high-risk' normal pregnancy (HR-NP), and women who developed gestational hypertension (GHD). *Significantly different from pre-pregnancy, $P<0.05$. $^{\alpha}$Significantly different than LR-NP, $P<0.05$. $^{\beta}$Significantly different from HR-NP, $P<0.05$.

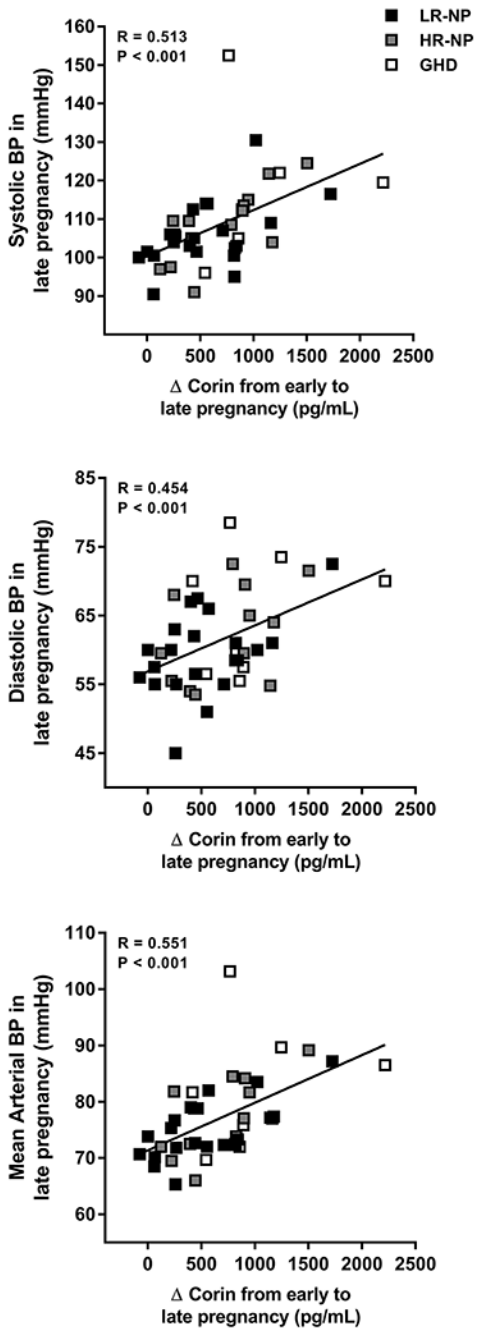

Figure 4.

Relationship between the change in corin from early- to late-pregnancy and resting blood pressure (BP) in late-pregnancy in ‘low-risk’ normal pregnancy (LR-NP), ‘high-risk’ normal pregnancy (HR-NP), and women who developed gestational hypertension (GHD).

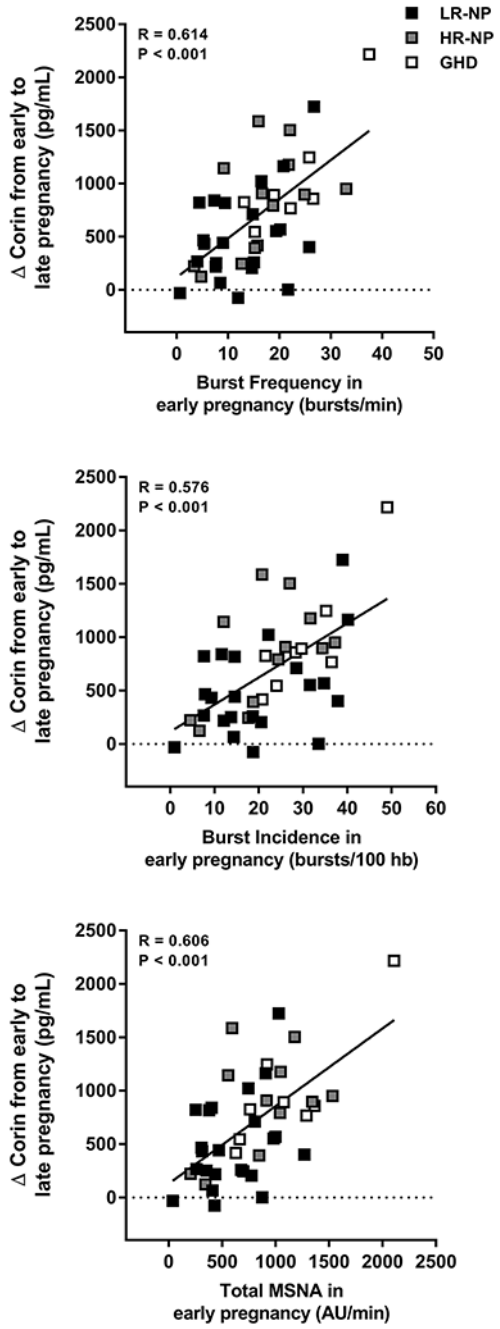

Figure 5.

Relationship between muscle sympathetic nerve activity (MSNA) in early-pregnancy and the change in corin from early- to late-pregnancy in 'low-risk' normal pregnancy (LR-NP), 'high-risk' normal pregnancy (HR-NP), and women who developed gestational hypertension (GHD).

Table 1.

Participant Characteristics

Characteristic	All (N=44)	LR-NP (n=23)	HR-NP (n=13)	GHD (n=8)
Gestation (wks)				
Pre	–	–	–	–
Early	7.2±0.2	6.8±0.3	7.2±0.5	8.2±0.7
Late	34.1±0.2	34.4±0.2	33.8±0.4	33.8±0.5
Post	8.3±0.2	8.3±0.3	8.6±0.4	8.0±0.5
Age (yrs)				
Pre	30±0.9	30±0.9	31±1.2	29±1.5
Early	30±0.7	31±0.9	31±1.2	29±1.5
Late	31±0.7	31±0.9	32±1.2	30±1.5
Post	31±0.6	31±0.9	32±1.2	30±1.5
Height (cm)				
Pre	163.8±1.2	163.8±1.6	163.4±2.1	164.2±2.7
Early	163.4±1.2	163.4±1.6	162.6±2.1	164.3±2.7
Late	163.8±1.2	163.9±1.6	163.1±2.1	164.6±2.7
Post	163.5±1.2	163.6±1.6	162.9±2.1	164.1±2.7
Weight (kg)				
Pre	73.3±3.0	60.5±3.8	71.3±5.0	88.0±6.3 †‡
Early	74.4±2.9	61.9±3.7	72.3±4.9	89.2±6.3 †‡
Late	85.6±2.9 *	73.1±3.7 *	82.3±5.0 *	101.3±6.3 *†‡
Post	78.6±2.9 *	66.4±3.7 *	75.6±4.9 *	93.94±6.3 *†‡
Racial Origin n (%)				
Caucasian	26 (59.1)	10 (43.5)	11 (84.6)	5 (62.5)
African American	5 (11.4)	3 (13.0)	–	2 (25.0)
Asian	8 (18.2)	7 (30.4)	–	1 (12.5)
Hispanic	5 (11.4)	3 (13.0)	2 (15.4)	–

Values are mean ± SEM. LR-NP, 'low-risk' normal pregnancy; HR-NP, 'high-risk' normal pregnancy; GHD, gestational hypertensive disorder.

* Significantly different from pre-pregnancy, $P<0.01$.

† Significantly different than LR-NP, $P<0.05$.

‡ Significantly different than HR-NP, $P<0.05$.