Role Of Corin In Blood Pressure Regulation In Normotensive And Hypertensive Pregnancy

By: Mark B. Badrov, Sun Young Park, Jeung-Ki Yoo, Michinari Hieda, Yoshiyuki Okada, Sara S. Jarvis, **Abigail S. Stickford**, Stuart A. Best, David B. Nelson, & Qi Fu

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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 (BP) regulation throughout pregnancy remains unclear. We investigated the time course of change in blood corin content in relation to BP and sympathetic nerve activity throughout pregnancy. Forty-four women (29±0.9 years) 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 8 developed gestational hypertension. BP, heart rate, muscle sympathetic nerve activity, and serum corin were measured before pregnancy, during early (4–8 weeks) and late pregnancy (32–36 weeks), and postpartum (6–10 weeks). Overall, compared with prepregnancy, corin remained unchanged during early pregnancy, increased markedly during late pregnancy ($P<0.001$), and returned to prepregnancy levels postpartum. 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 versus Δ486±79 pg/mL; $P<0.05$). Throughout pregnancy, BP 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 BP ($R=0.454$–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 BP regulation throughout normotensive and, especially, hypertensive pregnancy and may represent a promising biomarker for determining women at high risk of adverse pregnancy outcome.

Key Words: blood pressure ■ hypertension ■ pregnancy ■ risk ■ sympathetic nerve activity ■ women

Pregnancy-induced hypertensive disorders (ie, gestational hypertension and preeclampsia), which occur in ≈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 (GHDs) 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 cause of GHDs remain elusive, owing largely to the heterogeneous and multifactorial 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, preclinical 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 ANP (atrial natriuretic peptide) from its precursor peptide (ie, 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 (ie, 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 preeclampsia and hypertensive pregnancy; specifically, uterine *Corin* mRNA

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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 preeclamptic 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 (ie, 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 GHDs, 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 8 weeks of pregnancy participated in the current investigation after providing informed written consent. Participants were nonsmokers and free of overt disease. Exclusion criteria included chronic hypertension, recreational drug use or hormonal contraceptives within the previous 6-months, hormonal fertility treatment or supplement use, and 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. After term, participants were divided into 3 groups: (1) those women with low-risk (ie, no personal history of hypertensive pregnancy) normal pregnancies (LR-NP; n=23); (2) those women with high risk (ie, personal history of hypertensive pregnancy), yet normal pregnancies currently (HR-NP; n=13); and (3) those women who developed GHD after their late pregnancy testing (n=8).[21] Of the 8 women who developed gestational hypertension, 6 had a history of hypertensive pregnancy. Within the HR-NP group, 8 women had a personal history of gestational hypertension, 3 had a personal history of preeclampsia, 1 had a personal history of eclampsia, and 1 had a personal history of HELLP syndrome (a variant of preeclampsia 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 (ie, systolic BP ≥140 and diastolic BP ≥90 mm Hg) at ≥20 weeks of gestation in the absence of proteinuria or new signs of end-organ dysfunction. All 8 women who developed gestational hypertension during their pregnancies did so after their late pregnancy testing visit (see below). None of the women in the present study developed preeclampsia. Normal pregnancy was defined as those with the absence of GHDs or other pregnancy-related morbidities (ie, gestational diabetes mellitus).

Study Design and Protocol

Women were tested before pregnancy (midluteal phase; n=25), during early (4–8 weeks gestation; n=44) and late (32–36 weeks gestation; n=44) pregnancy, and postpartum (6–10 weeks postdelivery; n=43). Before each testing day, participants adhered to a 2-day isocaloric constant diet consisting of 150 mEq sodium, 100 mEq potassium, and 1000 mg calcium, whereas water intake was ad libitum. Experiments were performed ≥2 hours after a light breakfast, and participants abstained from caffeine and alcohol for ≥48 hours and strenuous exercise for ≥24 hours before study participation. Studies were conducted in a quiet, environmentally controlled laboratory with an ambient temperature of ≈25°C. All repeat testing was conducted at the same time of day. Pregnancy was confirmed each testing day by the measurement of β-human chorionic gonadotropin 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. After 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 after 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 3 BP measurements was 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 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 anticorin antibody. Next, serum samples or recombinant human corin protein standards were added and incubated at room temperature for 2 hours. The plates were washed 5× with a wash buffer, and a biotinylated antihuman corin antibody was added and incubated for another 2 hours. After 5 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), 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 GHDs 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 1-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 nonlinear, 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. 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 $P<0.001$ versus pre); however, the magnitude of weight gain was not different between groups ($P>0.05$).

Compared with prepregnancy, corin levels remained unchanged during early pregnancy, increased markedly during late pregnancy ($P<0.001$), and returned to prepregnancy levels after 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 versus 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. Before 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 $P<0.05$ versus early) and returned to prepregnancy levels after delivery (all $P>0.05$ versus 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 ($P<0.05$ versus pre), increased from early to late pregnancy ($P<0.05$ versus early), and remained at prepregnancy levels postpartum ($P>0.05$ versus pre). In women who developed GHD, systolic BP was greater than LR-NP throughout early and late pregnancy and postpartum, whereas diastolic BP and mean arterial BP were elevated at late and postpregnancy (all $P<0.05$). Furthermore, after 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 $P<0.05$ versus pre). After delivery, HR was decreased below prepregnancy levels in LR-NP and HR-NP (both $P<0.05$ versus pre) but was not different in GHD ($P>0.05$ versus pre). Throughout pregnancy, both HR-NP and GHD groups had greater resting HR than LR-NP (all $P<0.05$).

Table. Participant Characteristics

Characteristic	All (N=44)	LR-NP (n=23)	HR-NP (n=13)	GHD (n=8)
Gestation, wk				
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, y				
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 (%)				
White	26 (59.1)	10 (43.5)	11 (84.6)	5 (62.5)
Black	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. GHD indicates gestational hypertensive disorder; HR-NP, high-risk normal pregnancy; and LR-NP, low-risk normal pregnancy.

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

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

‡Significantly different from prepregnancy, $P<0.01$.

Figure 3 displays the changes in MSNA throughout pregnancy. Before 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 $P<0.05$ versus pre) yet returned to prepregnancy levels postpartum (all $P>0.05$ versus pre). Throughout early and late pregnancy, as well as postpartum, 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

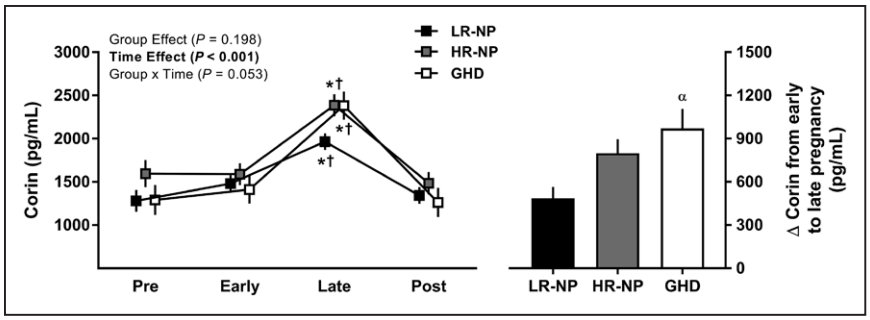

Figure 1. Maternal corin content throughout pregnancy. **Left**, Maternal corin content at pre, early, late, and postpregnancy. **Right**, The change in corin from early to late pregnancy in low-risk normal pregnancy (LR-NP), high-risk normal pregnancy (HR-NP), and women who developed gestational hypertensive disorder (GHD). *Significantly different from prepregnancy, $P<0.001$. †Significantly different from early pregnancy, $P<0.001$. αSignificantly different than LR-NP, $P<0.05$.

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 BP 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 nonpregnant 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 seems to be involved in the pathogenesis of hypertensive pregnancy. Specifically, when uterine corin levels are low, preeclampsia 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 seems that corin represents a key regulatory mechanism of arterial BP control throughout pregnancy in humans and, furthermore, may have a unique involvement in the cause 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 midpregnancy (16–20 weeks 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 with 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

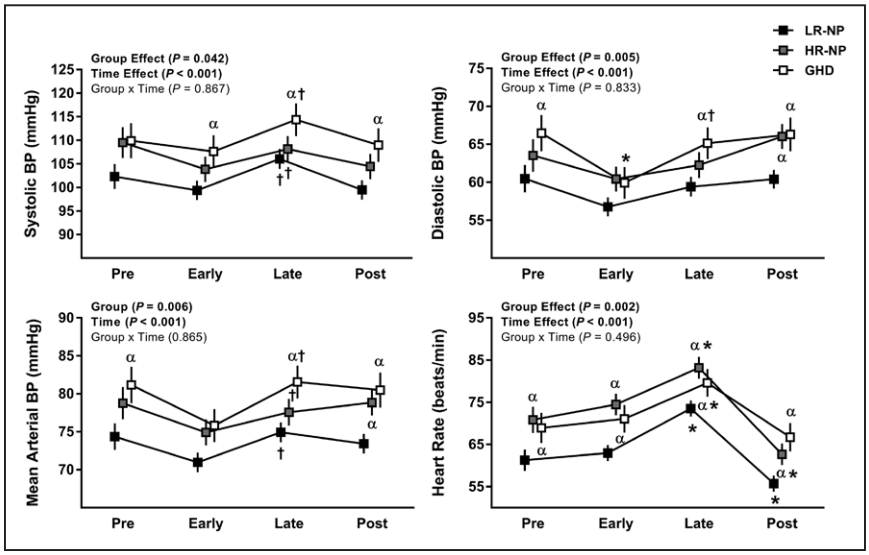

Figure 2. Resting blood pressure (BP) and heart rate at pre, early, late, and postpregnancy in low-risk normal pregnancy (LR-NP), high-risk normal pregnancy (HR-NP), and women who developed gestational hypertensive disorder (GHD). *Significantly different from prepregnancy, $P<0.05$. †Significantly different from early pregnancy, $P<0.05$. αSignificantly different than LR-NP, $P<0.05$.

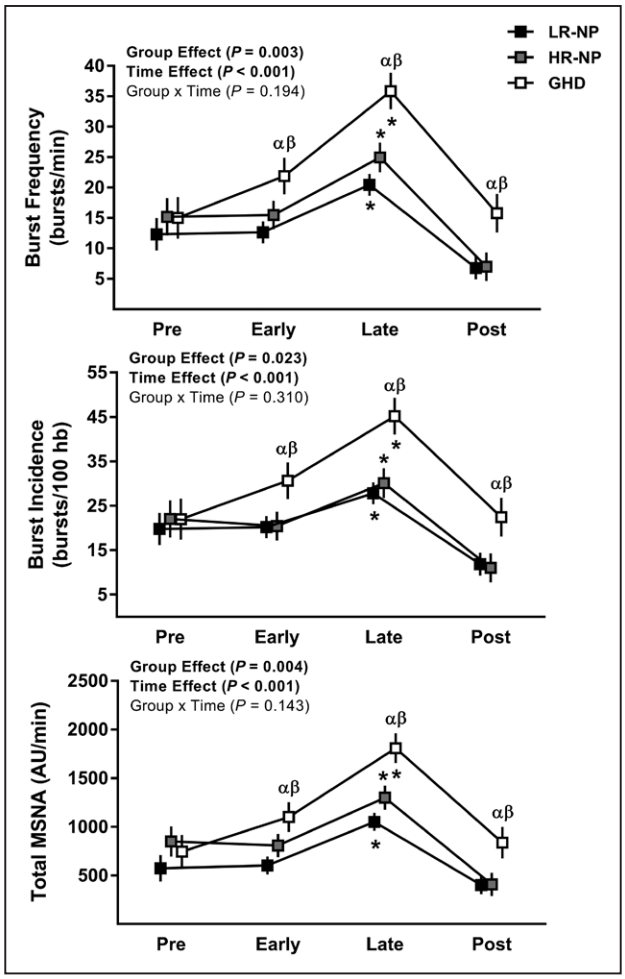

Figure 3. Muscle sympathetic nerve activity (MSNA) at pre, early, late, and postpregnancy in low-risk normal pregnancy (LR-NP), high-risk normal pregnancy (HR-NP), and women who developed gestational hypertensive disorder (GHD). *Significantly different from prepregnancy, $P<0.05$. αSignificantly different than LR-NP, $P<0.05$. βSignificantly different from HR-NP, $P<0.05$. AU indicates arbitrary units.

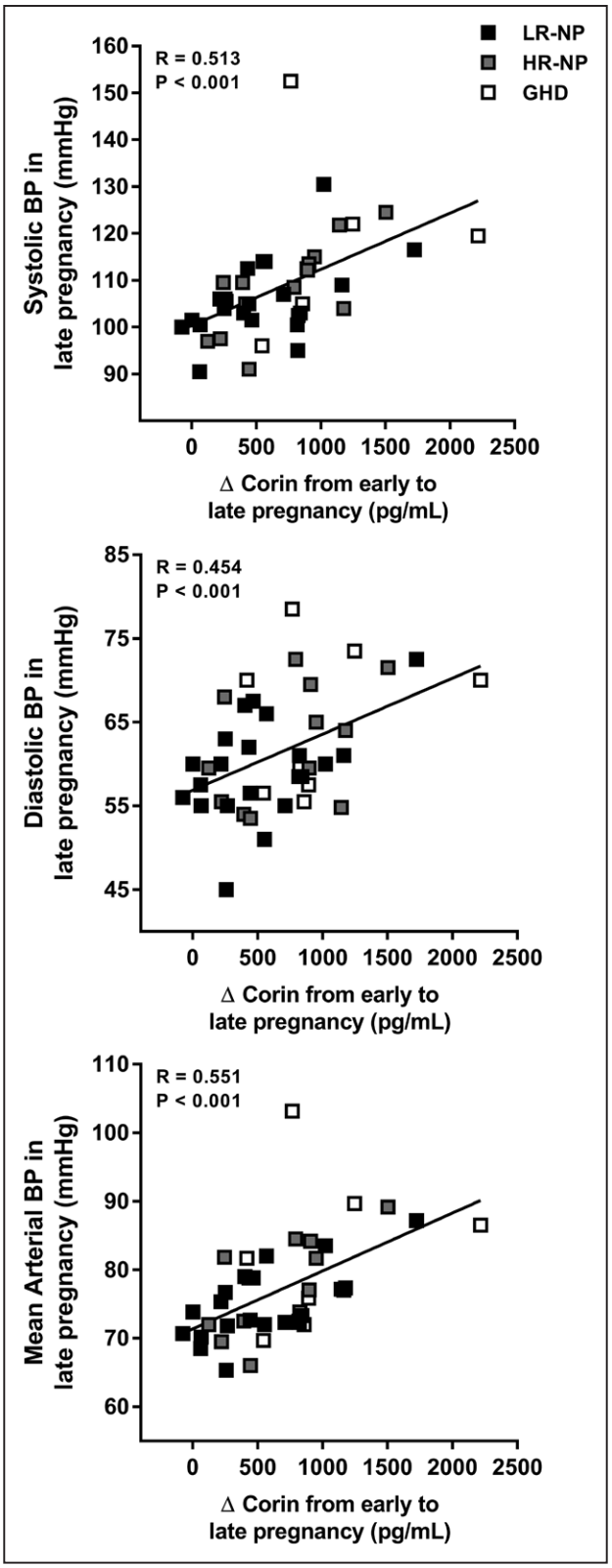

Figure 4. Relationship between the change in corin from early to late pregnancy and resting blood pressure (BP) in late pregnancy in low-risk normal pregnancy (LR-NP), high-risk normal pregnancy (HR-NP), and women who developed gestational hypertensive disorder (GHD).

and without preeclampsia, and not only were plasma corin levels higher in preeclamptic patients but also 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 preeclampsia than in normotensive women. Although 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 judgment as to the potential efficacy of corin as a biomarker of GHDs. In the only other longitudinal study, Khalil et al[16] found no differences in plasma corin levels at midpregnancy between women with gestational hypertension or preeclampsia at term and normotensive controls (was lower in preterm preeclampsia), yet levels in all groups increased rapidly as pregnancy progressed. Therefore, in line with our current findings, it seems 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

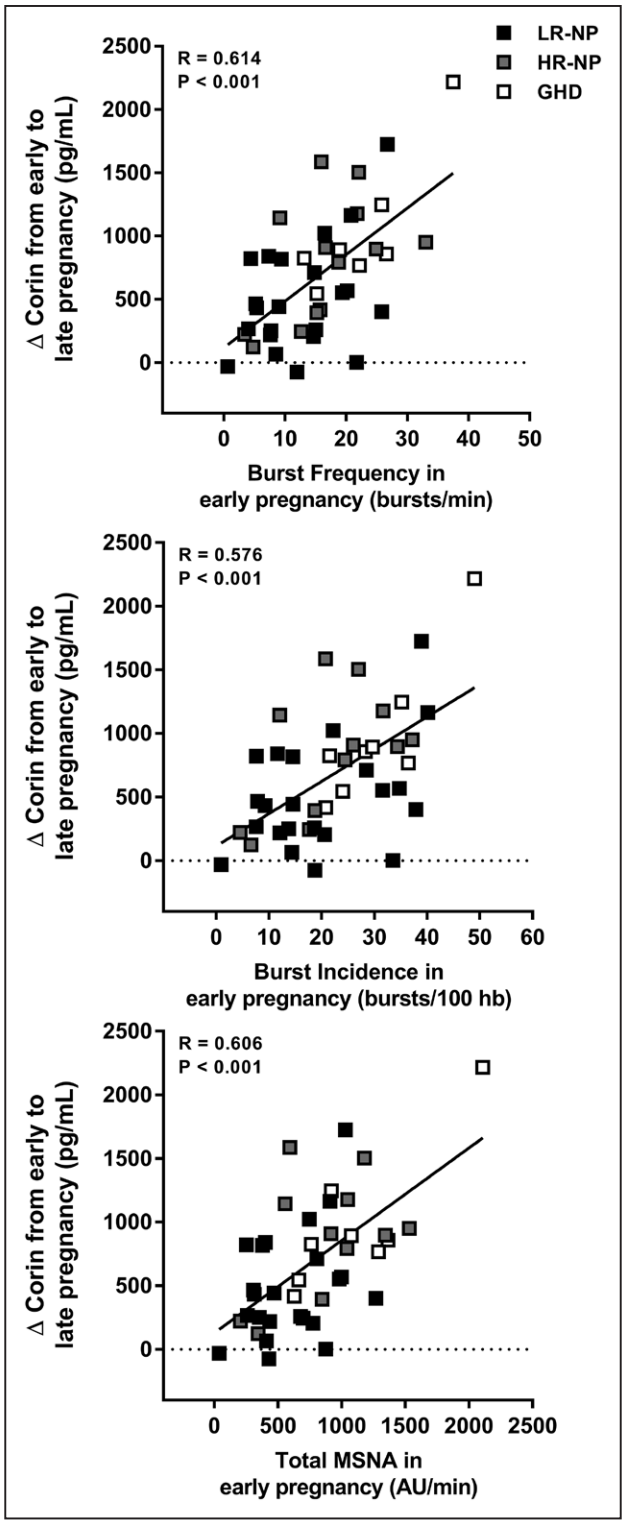

Figure 5. Relationship between muscle sympathetic nerve activity (MSNA) in early pregnancy and the change in corin from early to late pregnancy in low-risk normal pregnancy (LR-NP), high-risk normal pregnancy (HR-NP), and women who developed gestational hypertensive disorder (GHD). AU indicates arbitrary units.

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 preclinical 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%–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 prepregnancy levels. However, when excessive sympathetic activation occurs, GHDs 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] Although the reason for this discrepancy is unclear, it may be because of 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, preeclamptic and hypertensive pregnancies are characterized by low uterine *Corin* mRNA 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 (ie, 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 preeclampsia, NPR (natriuretic peptide receptor)-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 preeclampsia. 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 before 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 suggest 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 white women. Although we studied a limited number of Asians (n=8), blacks (n=5), and Hispanics (n=5), as compared to white women (n=26), there did not seem 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

GHDs 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, preeclampsia is now recognized as an independent risk factor for cardiovascular disease mortality.[43] Currently, management and treatment strategies remain limited, owing largely to the multifactorial nature of the disease. Fundamentally, GHDs 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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Disclosures

None.

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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.