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Pulse Pressure and Arterial Compliance Prior to Pregnancy and the Development of Complicated Hypertension during Pregnancy

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Abstract

We examined the relationship between prepregnant pulse pressure (PP), mean arterial pressure (MAP), cardiac output (CO)/PP, a measure of arterial compliance, and development of complicated hypertension during pregnancy (CH) with the goal of identifying a potential predictor of CH. Twenty nulliparous subjects were studied before pregnancy; seventeen had normal pregnancies (CTL) and three CH. Blood pressure monitoring was performed using tonometry. CO was determined by Doppler echocardiograph. Data are expressed as mean±SD. Prepregnant PP was significantly higher in CH subjects (CH: 58.3±6.3, CTL: 46.2±1.7 mmHg; $p = 0.02$). CO/PP was significantly lower in CH subjects (CH: 6.9 ± 1.8, CTL: 10.6 ± 2.8; $p = 0.04$). MAP was not significantly different. Increased PP before pregnancy may suggest increased risk for CH. With accurate prediction of CH before pregnancy initiation of preventative measures could begin earlier, either prior to, or in early pregnancy, potentially increasing preventative efficacy and decreasing CH.

Keywords

pulse pressure; arterial compliance; hypertension; pregnancy; preeclampsia

Introduction

Preeclampsia(PE) occurs in 3 – 5% of pregnancies and is a major cause of maternal mortality, morbidity, perinatal death and intrauterine growth restriction. It is characterized by hypertension and proteinuria. Physiologic manifestations include vascular resistance, reduced plasma volume, peripheral vasoconstriction, increased sympathetic tone and increased risk of cardiovascular disease later in life ^{1–11}. Increases in uterine vascular resistance coupled with endothelial dysfunction are associated with decreased vascular compliance and are considered to be likely contributors, respectively, to the fetal and

maternal manifestations of PE. Though it is widely accepted that mean arterial pressure (MAP) and pulse pressure (PP) are increased during PE, studies investigating cardiac output (CO) in relation to PE are controversial and show either increased or decreased CO, both prior to and during the early stages of disease^{3, 11–18}.

Given the deleterious effects of PE, detection of impending disease has been a focus of PE research. Most predictive indices such as uterine artery waveform analysis with evaluation of resistance index, pulsatility index and uterine notching, and assessment of systemic sympathetic tone as well as markers of placental dysfunction, have primarily been evaluated during pregnancy. Studies investigating the use of these indices as prognostic indicators of PE are conflicting and suggest that first trimester assessments are unreliable, suggesting that their value in predicting disease is limited^{11, 19–21}.

Pulse pressure has been used as a measure of cardiovascular risk as it is often elevated prior to adverse cardiovascular events^{22–24}. PP is an indicator of blood vessel elasticity where increased PP is a reflection of a stiffer vessel that exhibits reduced arterial compliance²⁴. Though PP is well established as an indicator of cardiovascular events, and increased vascular resistance and decreased compliance is evident in PE, evaluation of increased PP as a risk factor for the development of PE is limited. One study suggesting PP as a prognostic indicator of PE found that increased PP during early pregnancy is associated with increased risk of PE, but not gestational hypertension¹⁶.

Most PE research has focused on correlations between pregnancy phenotypes and the subsequent development of PE with the goal of finding reliable predictive indices in early pregnancy^{19, 25, 26}. We have hypothesized that a prepregnancy phenotype exhibited by poor vascular compliance is evident in women destined to develop PE²⁷. This prepregnancy phenotype contributes to an overall pregnancy phenotype that is associated with impaired adaptation to plasma volume expansion, leading to increased risk of developing PE. Therefore, we sought to examine the relationship between prepregnancy cardiovascular indices, including PP and arterial compliance, and the development of PE in nulliparous women.

Methods

Thirty four nulligravid women interested in conception were enrolled in this research study through an open advertisement. Women were provided with ovulation detection kits (Quidel Corporation, San Diego, CA) to assist with achieving a successful conception. All subjects were young (18–40) healthy, nonsmokers with regular menstrual cycles at the time of enrollment. None of the women had a history of hypertension, autoimmune disease, diabetes or other disorders known to affect blood pressure. Thirty women subsequently conceived. Eight subjects conceived before baseline pre-pregnancy studies were performed; one subject had a first trimester miscarriage; one subject was lost to follow-up. The remaining 20 subjects, all of whom conceived singleton pregnancies, had complete prepregnancy assessments and successful pregnancy outcomes, comprise the current report. Three women developed complicated hypertension during pregnancy. Two had classically defined preeclampsia with 24 hour urine collections demonstrating proteinuria >300 mg/dl and blood pressure >140/90 mmHg. The third woman had new onset third trimester, elevated blood pressure >140/90 mmHg, elevated liver enzymes, elevated uric acid concentration (>5mg/dl) and fetal growth restriction with iatrogenic delivery at 37 weeks. Women were enrolled consecutively over a 33 month period, from May 2004 through February 2007. Prior to each study visit subjects were provided a 3500-mg sodium-balanced diet for 72 hours. Each subject was asked to abstain from alcohol and caffeine for at least 24 hours before the study and to avoid the use of decongestants and nonsteroidal medications for at

least 48 hours before the study. All prepregnancy assessments were performed during the follicular phase. Assessments during pregnancy were performed between 11 and 15 menstrual weeks. Ovulation detection and early pregnancy ultrasound assessments were used to calculate gestational age. The research protocols were approved by the University of Vermont Human Investigational Committees. All women provided written informed consent.

Each periodic assessment was conducted between 8 AM and 10 AM. Subjects were admitted to the University of Vermont General Clinical Research Center on the day of the study after an overnight fast. For subjects' prepregnancy visit, first-void urine was obtained to confirm nonpregnant state. Following height and weight determination, subjects rested in the supine position for the remainder of the study with a minimum of 30 minutes prior to hemodynamic assessment.

Continuous noninvasive tonometric radial artery blood pressure monitoring was performed employing the Colin Pilot 9200 device (San Antonio, TX) with auto standardization to brachial artery measurements. Heart rate(HR)measurements were obtained by a standard3-lead electrocardiogram integrated with blood pressure measurements via the Colin device. Baseline blood pressure and HR were estimated following30 minutes of supine rest by calculating the MAP and RR interval from measurements during a sample time window.

Sympathetic responsiveness was estimated by measuring the blood pressure response to Valsalva maneuver in the supine position. Participants created a forced expiration for 20 seconds against a nonfixed low flow resistance to a pressure of 40 millimeters of mercury measured with an attached manometer. The calculated difference between the peak MAP measured at the end of late phase II response of the Valsalva maneuver and the trough MAP at the end of the early phase II response is termed the late phase II (phase IIL) response and reflects baroreceptor activity mediated by vascular α -adrenergic receptors. The calculated difference between baseline MAP and the top of phase IV represents the phase IV measurement and reflects β -adrenergic activity. Additional elements of this technique have been previously outlined ²⁸. Blood samples for catecholamine assessment were obtained as previously described ²⁹. Briefly, a superficial forearm vein was catheterized and the hand and forearm placed in a warming box set at 50°C to "arterialize" the venous samples ³⁰. Blood samples were collected in pre-iced tubes and immediately spun with plasma analyzed for free catecholamines (epinephrine, norepinephrine and dopamine).

Cardiac output(CO)was determined by Doppler echocardiographic examination. Doppler-derived forward stroke volume across the aortic valve was calculated as the product of the left ventricular outflow tract area and the outflow tract velocity time integral as assessed by pulsed Doppler using previously described methods ³¹. Five complete spectral envelopes with the largest Doppler shift were recorded and averaged for each patient. The Doppler stroke volume was calculated as the product of the outflow tract area and the velocity time integral. CO is expressed as L/minute after integration of stroke volume with pulse rate.

Pregnancy outcome was assessed by chart review and is reported as a function of prepregnancy physiologic condition.

Data Analysis

Hemodynamic and sympathetic tone measures were compared between women who developed complicated hypertension and those that did not based on the two sample unpaired t-test assessment. Where data did not pass the normality test the Mann-Whitney Rank Sum test was used. Changes in hemodynamic and sympathetic tone measures within the PE subjects between the prepregnant and first trimester visits were assessed. All

statistical analyses were performed using SigmaPlot 11.0 (Systat Software, Inc., San Jose, CA).

Results

Subject characteristics

All pregnancies were singletons, and the majority of the subjects were Caucasian, 90% (18/20). Clinical and demographic characteristics are presented in Table 1. There were no significant differences between non-hypertensive (CTL) and complicated hypertension (CH) subjects except in birth weight and birth weight percentile of the newborns (Table 1). CTL newborns had significantly higher birthweights and birthweight percentiles as compared to CH newborns. Two of the CH newborns were small for gestational age with 1 and 5% birthweight percentiles while the 3rd CH newborn was in the 30th percentile. CTL newborn birthweights ranged from the 15th to 95th percentile.

Cardiovascular assessments

Prior to pregnancy, HR was significantly higher in the CTL as compared to the CH while there was no difference in MAP (Table 2). PP was significantly increased in the CH subjects (Figure 1A, Table 2). Prepregnant CO tended to be lower in the CH subject (Table 2) and arterial compliance, as assessed by CO/PP, was significantly lower in the CH group (Figure 1B, Table 2).

First trimester CO tended to be lower in CH as compared to CTL (Table 3). There were no differences in MAP, HR, PP and CO/PP between groups.

Heart rate was significantly higher in the CH subjects during the first trimester as compared to prepregnant assessment ($p = 0.02$). There was no difference between HR time points in the CTL subjects ($p = 0.78$).

Sympathetic tone assessments

Prior to pregnancy, there were no differences in either the phase IIL or phase IV assessments between the CTL and CH groups. There were no differences in any of the catecholamine concentrations (Table 2). In the first trimester, phase IV was significantly higher in the CH subjects while there was no difference in phase IIL (Table 3). There were no differences in catecholamine concentration in the first trimester.

Discussion

Identification of a reliable predictor of PE risk is of great value for two reasons. One, if PE risk is determined early in pregnancy, or prior to pregnancy, preventative measures can be studied with high efficacy as the highest risk subjects can be enrolled in prospective prevention trials. Additionally, by examining and identifying reliable predisposing physiologic characteristics prior to, or during early, pregnancy the pathophysiology underlying PE may be more clearly elucidated.

Independent of pregnancy, pulse pressure is one of the indices often used as a predictor of cardiovascular risk as it is an indicator of vascular compliance and therefore associated with coronary heart disease, heart failure and stroke^{22–24, 34–38}. As arterial compliance is lowered in PE, pulse pressure has been suggested as a potential indicator of PE risk when evaluated during the first trimester and is known to be elevated during the third trimester in those who develop PE as well as after the onset of PE^{4, 16}. However, the few reports that describe the association of difference in pulse pressure in relation to PE are limited to

evaluating PP during pregnancy, thus, it is unknown whether this effect is due to a preexisting condition or a result of pregnancy. Here, we aimed to evaluate cardiovascular parameters and vascular function prior to pregnancy and during early pregnancy. We hypothesized that a prepregnancy phenotype exists that contributes to an inability to accommodate the cardiovascular challenges that pregnancy produces^{27, 29, 39}. We suggest that there are indicators that reflect inadequate adaptation to pregnancy specific physiologic challenges.

We found that PP was significantly higher in those women who went on to develop preeclampsia. Though others have reported elevated PP during the first trimester in those women who went on to develop PE¹⁶, the current study describes PP prior to pregnancy in the context of the development of PE. This finding is of particular interest as women who develop PE are at increased risk for cardiovascular disease later in life, and PP has been used as an indicator of cardiovascular risk independent of pregnancy^{5-7, 23, 34}.

Compliance is a measure of the change in pressure within a physical system relative to the change in volume. In normal pregnancy, arterial compliance is high to accommodate large increases in intravascular volume without associated changes in blood pressure^{2, 40}. However, in PE, arterial compliance is decreased^{1, 4}. We were interested in determining the relationship between arterial compliance prior to pregnancy and the development of CH. We used the calculation of CO/PP as an index of arterial compliance to assess cardiac blood volume pumped per minute relative to pressure. We found a significant decrease in CO/PP prior to pregnancy in the CH subjects as compared to CTL suggesting the existence of a pre-disease phenotype. This finding has potential biologic significance for the recurrence risk of preeclampsia in that we have shown that pregnancy itself appears to increase compliance with an effect that wanes over time, measured in years⁴⁰.

The ratio of stroke index (stroke volume corrected for body surface area)/PP has been used as a measure of arterial compliance and is also increased in the third trimester in those women with PE¹⁶. We found no difference between our CTL and CH subjects in stroke index/PP (data not shown). There were no differences in stroke volume/PP in CTL vs CH subjects at either time point. However, CO tended to be lower and HR was significantly lower in CH subjects at the first trimester assessment. Since we did not find any differences in stroke volume the decreased HR in the CH subjects is primarily responsible for the decreased CO. This observation is consistent with other studies showing decreased CO and HR during pregnancy complicated by IUGR^{12, 13}.

As PE is associated with increased sympathetic activity we were interested to determine if sympathetic activity would also be increased prior to pregnancy^{9, 41}. We evaluated sympathetic tone by Valsalva maneuver and catecholamine concentration. There were no differences between groups in catecholamine concentration (norepinephrine, epinephrine or dopamine) at either time point. This result is not surprising as catecholamine assessment is known to have limited reproducibility and sensitivity (reviewed by⁴²). Further, levels of catecholamines do not reflect the availability of receptors or receptor concentration, a key component of sympathetic activity. Therefore, we used the Valsalva maneuver to further determine sympathetic activity, specifically, α and β adrenergic activation. Interestingly, there were no differences prior to pregnancy in α -adrenergic (phase IIL) or β -adrenergic (phase IV) activation. As suggested in other reports, in early pregnancy, β -adrenergic activity was significantly increased in those who later developed CH. The increase in β -adrenergic responsiveness was likely responsible for the increase in HR from prepregnancy to early pregnancy. Sympathetic over activation has been characterized during PE, and has been identified during pregnancy in some women who will progress to PE. Schobel et al. showed that sympathetic overactivity during pregnancy is disproportionately increased when

compared to sympathetic tone in nonpregnant hypertensive women⁹. This finding is a potential reflection of underlying phenotypic predisposition evident in those who develop PE. Fischer et al reported increased sympathetic activity during pregnancy in women who had previous PE pregnancies, however, not all these women developed subsequent PE⁴¹.

Here, we present data that reinforces the hypothesis of a distinct prepregnancy phenotype in women destined to develop CH. These data suggest that a specific cardiovascular phenotype exhibited by increased pulse pressure and decreased arterial compliance exists prior to pregnancy and preeclampsia. We suggest that decreased arterial compliance and increased pulse pressure prior to pregnancy is evidence of a physiologic system that is primed for inadequate accommodation of the increased plasma volume demands of pregnancy. Measurable alterations in cardiovascular parameters such as pulse pressure and arterial compliance may contribute to a useful predictive index prior to the development of pregnancy complications and, as our data suggests, may even be useful prior to pregnancy. Ultimately it is critical to evaluate these prepregnancy physiologic observations and the ability of these observations to predict clinical disease in pregnancy. Specifically, the positive and negative predictive values for each physiologic variable, given specific predefined thresholds, will need to be examined. Our study was not intended to evaluate the predictive value of pulse pressure or CO/PP, therefore, we cannot comment on the predictive performance of these specific prepregnancy observations, however, our data strongly suggest that this should be addressed in future studies. Likewise, these observations provide preliminary data that may be useful in future studies examining the predictive value of prepregnant cardiovascular function for hypertensive pregnancy complications.

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Figure 1. Pulse pressure and arterial compliance prior to pregnancy in non-disease (CTL, n = 17) and complicated hypertensives (CH, n = 3)

Figure 1A: Pulse pressure is significantly higher in those women who developed complicated hypertension ($p = 0.02$). 1B: Cardiac output/pulse pressure, a measure of arterial compliance, is significantly lower in CH as compared to CTL ($p = 0.04$).

*Statistical significance determined by Student's t-test.

Table 1

Characteristics of the 20 women enrolled in this study.

Characteristic	CTL (n = 17)	CH(n = 3)	P value [§]
	Mean $\pm$ SD	Mean $\pm$ SD	
Maternal age (years)	28.9 $\pm$ 3.1	31.3 $\pm$ 2.1	0.20
Body mass index (kg/m ²)	23.7 $\pm$ 3.4	21.5 $\pm$ 1.5	0.30
Body surface area (m ²)	1.75 $\pm$ 0.14	1.65 $\pm$ 0.09	0.26
Prepregnancy cycle day	8 $\pm$ 4.1	7.7 $\pm$ 2.1	0.77
First trimester study day	93.3 $\pm$ 10.6	97 $\pm$ 13	0.60
Gestational age at delivery (weeks)	39.7 $\pm$ 1.2	38 $\pm$ 1.7	0.13 [*]
Birth weight (g)	3582 $\pm$ 396	2514 $\pm$ 728	0.001
Birth weight percentile	55.2 $\pm$ 24.7	12 $\pm$ 15.7	0.01

[§]Statistical significance determined by paired t-test except where indicated.

^{*}Mann-Whitney Rank Sum test performed to determine statistical significance.

Table 2

Prepregnancy comparisons of mean arterial pressure (MAP), heart rate (HR), pulse pressure (PP), cardiac output (CO), CO/PP, stroke volume (SV), SV/PP, catecholamine concentrations, phase IIL and phase IV assessments in control (CTL) and complicated hypertensives(CH). Data is expressed as mean $\pm$ SD.

Characteristic	CTL (n = 17)	CH (n = 3)	P value [§]
MAP(mmHg)	79.6 $\pm$ 10.1	88 $\pm$ 6.1	0.19
HR(beats/min)	73.2 $\pm$ 11.4	59.9 $\pm$ 0.6	0.0002
PP (mmHg)	46.2 $\pm$ 7.1	58.3 $\pm$ 11	0.02
CO (L/min)	4.8 $\pm$ 0.9	3.9 $\pm$ 0.8	0.13
CO/PP	0.11 $\pm$ 0.03	0.07 $\pm$ 0.02	0.04
SV (mL/beat)	66.4 $\pm$ 14.7	65.7 $\pm$ 13.9	0.94
SV/PP	1.48 $\pm$ 0.42	1.15 $\pm$ 0.32	0.21
Phase IIL (mmHg)	22.1 $\pm$ 9.8	25.3 $\pm$ 6.7	0.60
Phase IV(mmHg)	20.5 $\pm$ 9.1	15 $\pm$ 11.5	0.36
Epinephrine (pg/mL)	31.1 $\pm$ 13.5	29.3 $\pm$ 31.8	0.86
Norepinephrine (pg/mL)	241.1 $\pm$ 78.2	249.7 $\pm$ 48.7	0.86
Dopamine (pg/mL)	12.4 $\pm$ 6.8	12.0 $\pm$ 3.4	1.0*

[§] Statistical significance determined by Student's t-test except where indicated.

* Mann-Whitney Rank Sum test performed to determine statistical significance.

Table 3

First trimester comparisons of mean arterial pressure (MAP), heart rate (HR), pulse pressure (PP), cardiac output (CO), CO/PP, stroke volume (SV), SV/PP, catecholamine concentrations, phase IIL and phase IV assessments in control (CTL) and complicated hypertensives (CH). Data is expressed as mean $\pm$ SD.

Characteristic	CTL (n = 17)	CH (n = 3)	P value [§]
MAP (mmHg)	72.2 $\pm$ 6.4	77.7 $\pm$ 7.1	0.21
HR (beats/min)	71.4 $\pm$ 8.6	73.8 $\pm$ 6	0.28*
PP (mmHg)	49.1 $\pm$ 6.7	46.7 $\pm$ 6.4	0.57
CO (L/min)	5.4 $\pm$ 1	4.3 $\pm$ 1	0.10
CO/PP	0.11 $\pm$ 0.03	0.09 $\pm$ 0.01	0.23*
SV (mL/beat)	74.9 $\pm$ 13.3	59.4 $\pm$ 20.1	0.11
SV/PP	1.07 $\pm$ 0.25	0.82 $\pm$ 0.36	0.17
Phase IIL (mmHg)	23.5 $\pm$ 11.2	24 $\pm$ 10.1	0.94
Phase IV (mmHg)	17.4 $\pm$ 7.9	30.3 $\pm$ 10.1	0.02
Epinephrine (pg/mL)	20.5 $\pm$ 13.9	20.33 $\pm$ 22.3	0.58*
Norepinephrine (pg/mL)	231.9 $\pm$ 77.4	236.7 $\pm$ 23.9	0.92
Dopamine (pg/mL)	9.7 $\pm$ 6.9	5 $\pm$ 0	0.20*

[§]Statistical significance determined by Student's t-test except where indicated.

* Mann-Whitney Rank Sum test performed to determine statistical significance.