Cardiovascular Risk Factors One Year After a Hypertensive Disorder of Pregnancy

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Abstract

Objective: To identify differences in women's cardiovascular risk, independent of obesity, one year after delivery of a pregnancy complicated by a hypertensive disorder of pregnancy (HDP).

Methods: We compared traditional and novel cardiovascular risk factors of women recruited at delivery following the diagnosis of an HDP with those of women with uncomplicated pregnancies, at 3 months and 12–18 months postpartum. Measures included blood pressure, fasting lipids, inflammatory biomarkers, and measures of insulin resistance. Multiple linear regressions were used to adjust for body mass index (BMI) and other characteristics.

Results: We studied 71 subjects: 31 women with HDP and 40 with an uncomplicated pregnancy. There were no significant differences between groups for total cholesterol, HDL-c, LDL-c, triglycerides, HgbA1c, or homeostasis model assessment-estimated insulin resistance. Values for tumor necrosis factor- α were significantly higher in the HDP group ($p < 0.01$), while those for interleukin-6 and c-reactive protein were not. A diagnosis of HDP was associated with a 9 mm Hg difference in systolic blood pressure at both 3 months and 1 year, after adjustment for age, BMI, race, family history of cardiovascular disease, tobacco use, and insurance.

Conclusions: Women with HDP had significantly higher blood pressure 3 months and 1 year after delivery, independent of obesity. There were no significant differences in lipids or measures of insulin resistance after adjusting for BMI. Elevated blood pressure may account for the observed associations between HDP and future cardiovascular disease.

Introduction

HYPERTENSIVE DISORDERS OF PREGNANCY (HDP) occur in 5%–7% of pregnancies and are a leading cause of morbidity and mortality for mothers and their offspring.¹ Beyond pregnancy, historical cohort studies have revealed a link between HDP and future risk of cardiovascular disease (CVD),^{2–5} with estimates suggesting affected women have a four-fold increased incidence of chronic hypertension and twice the risk of CVD mortality when compared with women who had healthy pregnancies.^{2,6,7} This association may be due to the effects of the pregnancy, or instead reflect shared common risk factors.^{4,8} Recognition of this relationship has prompted recommendations, by the American Heart Association and others, to screen and address modifiable CVD risk factors of women who report a history of HDP.^{9,10}

Observational evidence highlights the importance of CVD risk factors accumulated during young adulthood.^{11,12} A small number of factors, including age, blood pressure, fast-

ing lipids, tobacco use, and diabetes, account for 75%–85% of CVD risk for populations; the measurement of novel biomarkers can help clarify mechanistic pathways involved in the development of CVD risk factors and add predictive value to standard models.^{13,14} A careful examination of these classical and novel CVD risk factors among women with a recent diagnosis of HDP is therefore of great interest and relevant to furthering our understanding of their future risk.

Evidence of adverse lipid profiles and measures of insulin resistance among women affected by HDP, but not differences in inflammatory measures, was provided by a 2012 systematic review and meta-analysis.¹⁵ Unfortunately, the potential confounding effects of obesity could not be accounted for in their analysis of the pooled data because of differences in how adjustments were handled by the included studies. Because pre-pregnancy obesity is associated with an increase in the risk of HDP,^{1,16} some of the differences detected in CVD risk factors may be related to underlying obesity rather than the pregnancy complication itself. Recently, two small prospective studies of

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women after HDP reported a higher prevalence of both chronic hypertension (CHTN) and metabolic syndrome within several years of an affected pregnancy.^{7,17–18} However, an earlier large prospective study of women 16 years after delivery found adjustment for body mass (BMI) attenuated the observed associations of HDP with lipids and diabetes, though differences in BP remained.¹⁹ Therefore, it remains unclear which CVD risk factors are independently linked to this pregnancy complication and if other mechanistic pathways are also involved.

The purpose of this study was to determine if differences in traditional and novel CVD risk factors one year after delivery of a pregnancy complicated by HDP are independent of obesity. To better account for the effects of obesity found in earlier studies, we used an equally obese comparison group of postpartum women without HDP.

Materials and Methods

Setting and subject recruitment

The source population for this study was a prospective cohort recruited during 2011–2012 from the postpartum service of an academic community hospital developed to study health services delivery following a live birth among women with and without complicated pregnancies. Approximately 85% of babies in the region are born at this center, where approximately 60% of mothers are privately insured and 25% are non-Hispanic African American. Because half the women with pregnancy complications were obese and African American women were overrepresented, we ensured a comparable control group by stratifying their recruitment into four pre-specified groups based on obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) and race: obese African American, nonobese African American, obese not African American, and nonobese not African American. Women < 18 years of age, non-English speaking, or who had diabetes mellitus prior to pregnancy were excluded.

Subjects were recruited to participate in 3-month and 1-year study visits if they had consented to further contact and were not pregnant. A follow-up interview was conducted and physical measures were collected at a 3-month visit. A more detailed interview and physical examination took place 12–18 months after delivery of the index pregnancy, referred to as the 1-year visit. At this visit, subjects were instructed to arrive after an overnight fast and to hold any antihypertensive or decongestive medications and any products containing nicotine or caffeine until completion of the study visit. Blood and urine were collected. Participants were compensated for their time completing the follow-up study visits. This study was approved by the Christiana Care Health System Institutional Review Board and all subjects provided written consent.

In this study, we compared outcomes of women with a pregnancy complicated by HDP to those in the uncomplicated control group. HDP was confirmed by review of the hospital obstetrical records. Women with a diagnosis of CHTN or who had a diagnosis of gestational diabetes were excluded from this analysis. We have previously reported average measures of blood pressure and inflammatory markers for a slightly larger sample drawn from this cohort.²⁰

Measures

A HDP was defined as new-onset blood pressure (BP) $\geq 140/90 \text{ mm Hg}$ after 20 weeks gestation as documented by

the admitting clinician and review of inpatient records. For the subgroup analysis preeclampsia was differentiated from gestational hypertension by the reporting in the medical record of proteinuria $\geq 300 \text{ mg}$ in a 24 hour urine, a blood pressure $\geq 160/110 \text{ mm Hg}$ on two or more occasions, or signs and symptoms of severe preeclampsia including thrombocytopenia or evidence of hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome.²¹

Primary outcomes were blood pressure (BP), a diagnosis of chronic hypertension (CHTN), and metabolic syndrome at the 1-year visit. A subject was considered to have CHTN if they were taking an antihypertensive medication or if their systolic BP or diastolic BP were greater than 140 or 90 respectively, at the 1-year visit. Metabolic syndrome was defined by the presence of three of the five: waist circumference ≥ 35 inches, triglycerides $\geq 150 \text{ mg/dL}$, HDL-c $< 50 \text{ mg/dL}$, glucose $\geq 100 \text{ mg/dL}$, and systolic BP $\geq 130 \text{ mm Hg}$ or diastolic BP $\geq 85 \text{ mm Hg}$.²² Measures of inflammation included c-reactive protein (hsCRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α); measures of insulin resistance included hemoglobin A1c (HgbA1c) and homeostasis model assessment–estimated insulin resistance (HOMA-IR) calculated from fasting glucose and insulin.²³ Covariates included age and BMI at the time of the 1-year visit, family history of CVD in a first degree relative, and tobacco use assessed as a self-reported ever/never smoked. Race and insurance status were also included in an effort to account for the effects of the social determinants of health.²⁴

Standardized interviews were conducted 1–2 days postpartum, at a 3-month visit, and again at the 1-year visit. Age was in years at the time of the 1-year study visit, and race was self-reported and dichotomized for regression analysis as African American versus other. Interval medical history included patient-reported information about current use of medications to treat hypertension. Insurance was based on health insurance at the time of the delivery and dichotomized as privately insured versus Medicaid or self-pay. Family history of CVD was defined as a self-reported history of CVD in a first-degree relative.

Physical measures reflecting blood pressure and adiposity were collected at the 3-month and 1-year study visits using standard procedures. Peripheral blood pressure was measured using a hospital-grade, automated oscillometric device (Welch Allyn) with patients rested in a seated position using patients' dominant arm supported at heart level. Patients were seated for a minimum of 10 minutes prior to the first measurement and each of the three measures were made 3 minutes apart. Height was measured to the nearest half inch. Waist circumference was recorded using a standard tape measure at the point just above the lateral aspect of the patient's iliac crest. Body mass at the study visits were measured with patients' shoes and heavy clothing removed, using a mechanical weigh beam scale (Detecto). BMI was calculated in kg/m^2 . Prepregnancy weight was self-reported.

Three biological markers (hsCRP, hs-TNF- α , and IL-6) known to be associated with CVD risk related to inflammation, dyslipidemia, and insulin resistance¹⁴ were measured at the 1-year visit using commercially available enzyme-linked immunosorbent assays (R&D Systems). All assays were performed according to the manufacturer's instructions at the University of Delaware Neuroendocrine Core Lab. All data was collected and analyzed on a BioTek Synergy 2 plate reader equipped with Gen 5 data analysis software. The lowest levels of detection were

TABLE 1. CHARACTERISTICS OF THE PARTICIPANTS WITH AND WITHOUT A HYPERTENSIVE DISORDER OF PREGNANCY

	Control	Hypertensive disorder of pregnancy	p-Value
Number of participants (n=71)	40	31	
<i>CVD risk factors</i>			
Maternal age, years	30.6 (5.2)	32.0 (6.6)	0.44
Smoking, n (%)	12 (30.0)	10 (32.3)	0.84
Family history of CVD, n (%)	19 (47.5)	7 (22.6)	0.03
<i>Sociodemographic characteristics</i>			
African American race, n (%)	11 (27.5)	7 (22.6)	0.64
Privately insured for delivery, n (%)	25 (62.5)	26 (83.9)	0.05
<i>Prepregnancy characteristics and outcomes</i>			
Obese prior to pregnancy, n (%)	20 (50.0)	16 (51.6)	0.89
BMI prepregnancy, kg/m ²	30.2 (8.0)	30.0 (8.2)	0.94
Nulliparous, n (%)	15 (37.5)	14 (45.2)	0.60
Delivered preterm, n (%)	2 (5.0)	6 (19.4)	0.06
Birth weight, grams	3554.5 (423.3)	3336.6 (544.0)	0.07
Low birth weight, n (%)	0 (0)	2 (6.5)	0.10

Values are given as mean $\pm$ standard deviation for continuous data; n (%) for categorical data. Significance testing using *t*-test and chi-squared for continuous and categorical data respectively using control as the referent group.

BMI, body mass index; CVD, cardiovascular disease.

0.11 ng/mL for hsCRP, 0.52 pg/mL for TNF- α and 0.70 pg/mL for IL-6. The intra- and inter-assay coefficients of variation were less than 10%. Fasting lipid panels, glucose, insulin, and HgbA1c were analyzed the day of the study visit at the institutional Clinical Laboratory Improvement Amendments (CLIA)-certified clinical laboratory. Insulin resistance was estimated using HOMA-IR, calculated as [(fasting insulin $\times$ fasting glucose)/405].²³ Framingham Score and Reynold's Risk Score, which also incorporates hsCRP, were calculated using standard equations.^{25,26}

Data were nearly complete for all measures. One subject had missing data for the inflammatory markers due to unavailability of blood and was excluded from that analysis; three subjects had missing measures for BP at the 3-month study visit.

Statistical analysis

Descriptive statistics were used to compare characteristics of the groups at the baseline, 3-month, and 1-year visits,

TABLE 2. COMPARISON OF THREE-MONTH AND ONE-YEAR MEASURES FOR PARTICIPANTS WITH AND WITHOUT A HYPERTENSIVE DISORDER OF PREGNANCY

	Control	Hypertensive disorder of pregnancy	p-Value
Number of participants	40	31	
<i>Three-month visit</i>			
SBP at 3 months, mm Hg	108.7 (8.9)	117.2 (10.6)	<0.01
DBP at 3 months, mm Hg	71.0 (5.5)	78.3 (8.3)	<0.01
<i>One-year visit</i>			
SBP at 1 year, mm Hg	111.4 (10.0)	119.4 (11.6)	<0.01
DBP at 1 year, mm Hg	72.9 (7.4)	78.0 (8.9)	0.01
Change in SBP 3 months – 1 year, mm Hg	3.3 (9.2)	2.4 (10.3)	0.70
Change in DBP 3 months – 1 year, mm Hg	2.3 (7.1)	–0.1 (10.1)	0.28
Hypertension or BP $\geq$ 140/90, n (%)	1 (2.5)	5 (16.1)	0.04
BMI, kg/m ²	31.9 (8.9)	31.4 (8.0)	0.80
BMI change from prepregnancy, kg/m ²	1.7 (3.2)	1.4 (2.9)	0.63
Waist circumference $\geq$ 35 inches, n (%)	25 (62.5)	20 (64.5)	0.86
Taking an antihypertensive medication, n (%)	0 (0)	1 (3.3)	0.26
Metabolic syndrome, n (%)	5 (12.5)	5 (16.1)	0.66
Framingham risk $\geq$ 1%, n (%)	8 (21.1)	6 (20.0)	0.91
Reynolds risk, % ^a	0.24 (0.23)	0.30 (0.46)	0.31

Values are given as mean $\pm$ standard deviation for continuous data; n (%) for categorical data. Significance testing using *t*-test and chi² for continuous and categorical data respectively using control as the referent group.

^aMedian (interquartile range) and Wilcoxon-Mann-Whitney rank sum test presented for nonparametric data.

DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 3. COMPARISON OF BIOMARKERS ONE YEAR AFTER DELIVERY OF THE PARTICIPANTS WITH AND WITHOUT A HYPERTENSIVE DISORDER

	Control	Hypertensive disorder of pregnancy	p-Value
Number of participants (n = 71)	40	31	
<i>Inflammatory biomarkers</i>			
TNF- α , pg/mL*	4.0 (5.3)	8.8 (13.2)	<0.01
hsCRP, ng/mL ^a	8.7 (3.4)	12.3 (15.7)	0.39
hsCRP > 3 ng/L, n (%)	23 (59.0%)	18 (58.1%)	0.94
IL-6, pg/mL	8.1 (2.5)	8.2 (2.4)	0.94
<i>Lipids</i>			
Total cholesterol	181.9 (29.1)	183.9 (31.7)	0.78
Triglycerides	92.9 (43.5)	96.6 (54.4)	0.76
HDL cholesterol	52.9 (9.2)	54.5 (12.9)	0.56
LDL cholesterol	110.5 (25.2)	110.2 (28.6)	0.96
<i>Glucose metabolism</i>			
HgbA1c	5.4 (0.4)	5.4 (0.4)	0.37
HOMA-IR	2.0 (1.6)	2.6 (1.9)	0.21

Values are given as mean $\pm$ standard deviation for continuous data; n (%) for categorical data. Significance testing using *t*-test and χ^2 for continuous and categorical data respectively using control as the referent group.

^aLog transformed for normality; transformation reversed for presentation.

HDL, high-density lipoprotein; HgbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment–estimated insulin resistance; hsCRP, c-reactive protein; IL-6, interleukin-6; LDL, low-density lipoprotein; TNF- α , tumor necrosis factor alpha.

reporting means and standard deviations or median and interquartile range where measures were not normally distributed. Significance testing was conducted using Student's *t*-test and chi-squared test for continuous and categorical measures respectively, comparing each exposure group with the uncomplicated control group. Select biomarkers were log transformed for normality prior to testing. The Wilcoxon-Mann-Whitney rank sum test was used for nonparametric measures.

Multiple linear regression models were used to adjust for the potentially confounding effects of traditional risk factors for HDP and CVD and included age, BMI, race, family history of cardiovascular disease, tobacco use, and insurance. Alpha <0.05 was considered significant.

We additionally explored possible heterogeneity between hypertension during pregnancy women with gestational hypertension and preeclampsia through a stratified analysis. All analyses were conducted using R version 2.15.3 (R Foundation for Statistical Computing).

Results

There were 71 subjects included in this analysis: 31 with HDP and 40 in the uncomplicated control group. The characteristics of the two groups are shown in Table 1. There were no significant differences between the groups in mean age, race, BMI prior to pregnancy or at the study visits, or percentage of women with a waist circumference 35 inches or more. The groups differed only in the higher percentage of women who were privately insured for the delivery in the HDP group ($p=0.05$) and more women in the uncomplicated control group who reported a family history of CVD ($p=0.03$). Pregnancy outcomes showed differences of marginal significance, with more preterm delivery and lower average birth weight among women in the HDP group, as expected. All of the women who delivered preterm had a diagnosis consistent with preeclampsia. Approximately half of the women in each group were obese, and rate of self-reported history of any tobacco use was 30% in each group.

Table 2 shows results of the physical measures at the 3-month and 1-year visits. Measures of both systolic BP and diastolic BP were significantly higher in the HDP group at both points in time, and there were no significant differences between the groups in the change in either measure from 3 months to 1 year for individuals (data not shown). Hypertension was more common in the HDP group at 1 year. There were no significant differences in the BMI, change in BMI from prepregnancy, waist circumference, or prevalence of metabolic syndrome. One subject, from the HDP group, was taking an anti-hypertensive medication at the time of the 1-year visit. There were no significant differences between

TABLE 4. LINEAR REGRESSION ESTIMATES OF THE ASSOCIATION OF HYPERTENSIVE DISORDERS OF PREGNANCY WITH BLOOD PRESSURE, AT THREE MONTHS AND ONE YEAR AFTER DELIVERY

Covariates	Three months		One year	
	SBP (mm Hg)	DBP (mm Hg)	SBP (mm Hg)	DBP (mm Hg)
HDP	8.98 (2.32)***	6.96 (1.64)***	9 (2.31)***	5.23 (1.86)**
Age, years	0.14 (0.19)	0.19 (0.13)	0.07 (0.19)	0.09 (0.16)
BMI, kg/m ²	0.53 (0.14)***	0.43 (0.1)***	0.69 (0.14)***	0.45 (0.11)***
African American race	1.23 (2.85)	0.57 (2.01)	4.01 (2.89)	2.77 (2.33)
Private insurance	2 (2.78)	0.77 (1.97)	0.23 (2.82)	−0.78 (2.27)
Family history of CVD	2.52 (2.44)	−1.14 (1.72)	2.02 (2.43)	−1 (1.96)
Tobacco use	−3.03 (2.58)	−0.59 (1.82)	−0.78 (2.52)	−0.72 (2.03)
Intercept	85.56 (7.27)***	51.34 (5.13)***	85.25 (7.42)***	56.2 (5.98)***
n	68	68	71	71
Adjusted R ²	0.32	0.38	0.40	0.28

Values are given as estimate (standard error).

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

the groups in either the Framingham Risk Score or the Reynolds Risk Score.

Table 3 shows results of the biomarkers measured at the 1-year visit. Values for TNF- α were significantly higher in the HDP group ($p < 0.01$), while those for IL-6 and hsCRP were not. There were no significant or marginally significant differences between groups for any of the lipid measures including Total-c, HDL-c, LDL-c, and triglycerides. Nor were there significant or marginally significant differences in HgbA1c or HOMA-IR.

The results of multivariable linear regression models predicting systolic BP and diastolic BP, adjusting for age, BMI, race, family history of cardiovascular disease, tobacco use, and insurance, are shown in Table 4. A diagnosis of HDP was associated with a 9 mm Hg difference in systolic BP when measured at both the 3-month and 1-year visits after adjustment for all factors in the model. BMI was also associated with all BP measures, and there were no significant associations of BP with other covariates. The values of the adjusted R^2 indicated excellent model fit.

Multivariable linear regression models of biomarkers are shown in Table 5, each adjusted for age, BMI, race, family history of cardiovascular disease, tobacco use, and insurance. The significant association of HDP with higher levels of TNF- α remained after adjustment, and there were no significant or marginally significant associations with the other biomarkers measured. As shown in the table, the variable most significantly associated with all other measures was BMI.

Exploration of differences between the subgroups of women with preeclampsia ($n = 15$) and gestational hypertension ($n = 16$) were conducted. We did not find any differences, but due to the small subgroups, power was insufficient to draw conclusions (results not shown).

Discussion

On average, blood pressure was higher among women with a diagnosis of HDP 3 months and 1 year after delivery, when compared to an uncomplicated control group with similar degree of obesity. However, there were no significant differences in fasting lipids, measures of insulin resistance, or two of three measures of inflammation nor differences in either the Framingham or Reynolds Risk Scores, likely related to the young ages of the subjects. Of interest, levels of TNF- α were higher in the HDP group after adjustment for multiple covariates, suggesting the potential additional importance of inflammatory pathways.

Unlike prior studies, we compared women who had a diagnosis of HDP to a control group of women who had uncomplicated pregnancies but the same degree of obesity.²⁷ Though a recent systematic review and meta-analysis found evidence of significant differences in lipids and measures of insulin resistance among women with HDP, their inability to adjust for BMI or other measures of adiposity may account for their different findings.¹⁵ Similarly, two prospective cohort studies of women during the early years after the pregnancy found an increased risk of hypertension, metabolic syndrome, glucose intolerance or insulin resistance; however, differences in BMI between affected and unaffected women were observed but not accounted for in the analysis.^{17,28} By better accounting for the effects of obesity and other potentially confounding factors, our findings suggest that elevated blood pressure uniquely differentiates

TABLE 5. LINEAR REGRESSION ESTIMATES OF THE ASSOCIATION OF HDP WITH INDIVIDUAL BIOMARKERS

Covariates	Inflammatory markers			Lipids			Glucose metabolism		
	TNF- α ^a	hsCRP ^a	IL-6	Total-c	TG	HDL-c	LDL-c	HgA1C	HOMA-IR
HDP	3.55 (1.49)**	1.26 (1.39)	-0.16 (0.65)	-3.77 (6.93)	-1.88 (11.08)	1.54 (2.59)	-4.9 (6.27)	-0.12 (0.1)	0.44 (0.38)
BMI, kg/m ²	1 (1.02)	1.12 (1.02)***	0.08 (0.04)*	0.89 (0.41)*	2.24 (0.65)**	-0.59 (0.15)***	1.03 (0.37)**	0.01 (0.01)*	0.1 (0.02)***
<i>n</i>	70	70	70	71	71	71	71	71	71
Adjusted <i>R</i> ²	0.1	0.34	-0.03	0.23	0.23	0.17	0.19	0.07	0.29

Values are given as estimate (standard error).

All regression models shown were also adjusted for age, African American race, insurance type, family history of CVD, and current tobacco use.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

^aLog transformed for normality; transformation reversed for presentation.

TG, triglycerides.

women who had a diagnosis of HDP. The absence of significant differences in most biomarkers also likely resulted from our use of a more comparable control group.

Our study provides evidence to support a confounding role for BMI, reinforcing the importance of accounting for obesity when investigating the relation of adverse pregnancy outcomes to long-term CVD risk. The strong relationship of BMI to blood pressure and other biomarkers within both groups emphasizes the important role of obesity in driving long-term CVD outcomes, independent of a HDP diagnosis.

A large body of observational research has demonstrated that the association of BP with CVD risk rises continuously and without a threshold.²⁹ For example, using Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure categories, “high normal” BP (130 to 139/85 to 89 mm Hg), when compared to normal (120 to 129/80 to 84 mm Hg), carried a 1.6–2.5 fold increase in risk of CVD.³⁰ If the increased BP we observed in affected women persists over the subsequent decades, it could account for the estimated two-fold greater risk of CVD identified in the historical cohort studies of women after preeclampsia and gestational hypertension.⁷

The significant difference in TNF- α is interesting and merits further investigation. A recent systematic review and meta-analysis found evidence of elevated TNF- α , IL-6, and IL-10 in women with preeclampsia, consistent with the inflammatory nature of the syndrome.³¹ Less is known about levels of inflammatory markers during the postpartum period or remote from pregnancy, though there are small studies suggesting higher levels of IL-6 and TNF- α .^{32,33} We found no differences in IL-6 or hsCRP between the two groups, both inflammatory markers considered to be potentially useful in prediction of future CVD.¹⁴ Each of these markers were significantly related to BMI; therefore, the absence of a difference could be due to the comparability of the BMI in both groups. On the other hand, measures of TNF- α were not related to BMI, but did differ between groups. These findings will need to be replicated in other studies to determine if TNF- α may play a role in vascular dysfunction after delivery, as has been suggested by small studies using noninvasive methods to measure endothelial dysfunction and arterial stiffness.^{34–36}

There are important limitations that should be considered when interpreting the results of this study. The small sample size precluded an analysis of subgroups of HDP and therefore we were unable to fully investigate heterogeneity between the groups of women with gestational hypertension and preeclampsia or differences related to measures of disease severity. This might have led to underestimate of associations with inflammatory and other biomarkers. In addition, most of the women with HDP delivered at term, therefore our findings may not apply to women with severe disease. The small sample size may also have limited our ability to detect small differences in biomarkers between the groups. However, this challenge was mitigated in part by the use of a more comparable control group. Lastly, blood pressure was recorded at a single visit and could be falsely elevated due to stress or anxiety of the visit.

Several important questions could not be addressed using this study design and which are critical to understanding of the impact of the pregnancy complication of CVD risk trajectory. Because we did not have prepregnancy measures, we could not determine if the pregnancy altered the BP or other

measures and thereby the CVD risk trajectory. The differences in BP were large and may have been present prior to pregnancy but did not lead to a diagnosis of CHTN because they failed to reach a diagnostic threshold for CHTN.

In summary, we found that women with HDP had significantly higher BP 3 months and 1 year after delivery, which was independent of BMI. There were no significant differences in lipids or measures of insulin resistance after accounting for differences in BMI, suggesting that BP may be a unique risk factor influencing future CVD risk among women after HDP. Though larger studies are needed to confirm these findings, they reinforce the importance of early assessment of BP and suggest a focus on the optimization of traditional CVD risk factors in women during the childbearing years. In addition, it is possible that the differences in BP measured during the postpartum period were present prior to pregnancy. Studies of women starting prior to conception are needed to explore the causal relationship between HDP and future hypertension and CVD.

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Author Disclosure Statement

No competing financial interests exist.

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