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Hypertension in pregnancy is associated with elevated C-reactive protein levels later in life

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Abstract

Objectives—We assessed if hypertension in pregnancy is associated with elevated CRP levels in later life, possibly reflecting an increased risk of CVD.

Background—Elevated C-reactive protein (CRP) levels have been associated with hypertension in pregnancy and with cardiovascular disease (CVD).

Methods—We studied 2463 women from the Genetic Epidemiology Network of Arteriopathy (GENOA) study. Subjects were categorized as nulliparous women (n=219), women with a history of normotensive pregnancies (n=1839), or women with a history of a hypertensive pregnancy (n=405). Using multiple linear regression models we compared mean CRP levels among the groups after adjusting for age, race, education, smoking, hypertension, personal history of CHD or stroke, diabetes, dyslipidemia, statins, hormone replacement therapy, and family history of CHD or stroke. As CRP levels may be influenced by body mass index (BMI), the model was fit both with and without adjusting for BMI.

Results—There was no significant difference in CRP levels between nulliparous women and those with a history of normotensive pregnancies, either with (p=0.82) or without (p=0.46) adjusting for BMI. In contrast, women with hypertensive pregnancies, compared to those with normotensive pregnancies, had higher CRP levels, both with (p=0.009) and without (p<0.001) adjusting for BMI.

Conclusions—A history of hypertension in pregnancy is associated with elevated CRP levels later in life, independent of traditional CVD risk factors and BMI. An elevated CRP may reflect an inflammatory state in women with a history of hypertensive pregnancy disorders who are at increased risk for CVD.

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Conflicts of Interest

For all authors none declared, no conflict of interest.

Keywords

hypertension; pregnancy; CRP; cardiovascular disease

Introduction

Heart disease remains the leading cause of death in women in the United States and globally [1]. Evaluation of cardiovascular disease (CVD) risk and preventative CVD measures in women need to be extended beyond the established CVD risk factor screening, to include pregnancy history [1, 2]. There is increasing evidence that hypertension in pregnancy is an under-recognized risk factor for CVD. Compared with women who have had normotensive pregnancies, those who are hypertensive during pregnancy are at greater risk of cardiovascular and cerebrovascular events years after their pregnancies [3–8]. A possible mechanism for this association is that hypertensive disorders of pregnancy and CVD share several common risk factors such as obesity, diabetes, and renal disease that contribute to endothelial dysfunction and lead to hypertension in pregnancy and CVD at different times in a woman's life. Alternatively, hypertension in pregnancy itself might modify the future risk of CVD by inducing long-term metabolic and vascular changes [9]. Regardless of the underlying mechanism, a biomarker that might identify women at increased CVD risk among those with a history of hypertensive pregnancies may contribute significantly to optimization of their clinical management.

With a growing body of evidence indicating that atherosclerosis is an inflammatory process, various markers of inflammation have been evaluated both for their potential atherogenic role and as predictors of increased risk of cardiovascular events [10, 11]. High-sensitivity CRP (hs-CRP) is a systemic inflammatory marker synthesized in the liver and is a component of the innate immune system. When measured by the highly sensitive assay, CRP has been associated with systemic inflammation [12], incident coronary heart disease (CHD) [13], and future cardiovascular events [14], independent of traditional risk factors [12, 15]. Evidence exists to support the role of CRP in predicting future cardiovascular events in women [12, 16–19]. It has been proposed that specific levels of hs-CRP <9.52 nmol/L, 9.52–28.6 nmol/L, and > 28.6 nmol/L correspond to low-, moderate-, and high-risk groups for future cardiovascular events, respectively [20].

The aim of this study was to assess in a large cohort of women if hypertension in pregnancy is associated with elevated CRP levels in later life, and if this association is independent of established CVD risk factors. We postulated that elevated CRP levels, which have been reported in preeclamptic pregnancies, may persist years after the affected pregnancies, thus serving as a biomarker of both an underlying inflammatory state, and an increased risk for CVD later in life.

Methods

Participants

The NHLBI Family Blood Pressure Program (FBPP) was a community-based study established in 1995 to investigate the genetics of hypertension in multiple racial groups [21]. It consisted of four different networks, all ascertaining families having individuals with elevated blood pressures or a genetic predisposition to hypertension [21]. The Genetic Epidemiology Network of Arteriopathy (GENOA) of the FBPP network had three field centers: one in Jackson, MS, which recruited African-Americans; one in Rochester, MN, which recruited non-Hispanic whites; and one in Starr County, TX, which recruited Mexican Americans. At the second GENOA study examination (2000–2004), the total female

population of the GENOA network was 2501. The present study included 2463 women who participated in the second GENOA study examination and had available CRP data

A questionnaire was administered to obtain participants' personal and family medical histories, including their use of prescription medications in the previous month; histories of menopause and hormone replacement were obtained from female participants. A history of a hypertensive disorder in pregnancy was confirmed by a standard pregnancy questionnaire that was previously validated [22]. Women were asked whether they had a pregnancy that lasted more than 6 months and whether or not they had developed hypertension during any of their pregnancies. Preeclampsia was defined either by self-report of this condition, or by self-report of hypertension and protein in the urine during the pregnancy. For the analyses, we grouped hypertension in pregnancy alone and preeclampsia together and refer to them as women with a history of at least one hypertensive pregnancy throughout the study.

Study visit

All individuals who participated in GENOA study examinations gave informed consent; the Institutional Review Board at each site approved all protocols. At the second GENOA study examination visit, systolic and diastolic blood pressures were measured using an automated oscillometric blood pressure measurement device using a consistent protocol across networks. Height was measured while participants were standing without shoes, with heels together, against a vertically mounted ruler, and weight was measured on a balance. BMI was calculated as weight (kg)/height (m).²

The diagnosis of hypertension was confirmed if a prior diagnosis and use of prescription anti-hypertensive medication were reported, or if the average systolic or diastolic blood pressures were at least 140 or at least 90 mm Hg, respectively. The diagnosis of diabetes was self-reported. The diagnosis of CHD was established by self-reports of a previous history of myocardial infarction, coronary bypass surgery, coronary angioplasty, balloon dilatation or stent placement, and the diagnosis of cerebrovascular disease was based on self-reports of stroke and/or cerebral hemorrhage. History of smoking was defined as having smoked more than 100 cigarettes in the past. Among smokers, pack-years were defined as the number of years smoked multiplied by the number of packs smoked per day. Pack-years were equal to 0 for non-smokers. The diagnosis of dyslipidemia was confirmed if one or more of the following criteria were met: use of lipid-lowering drugs or laboratory measurements during the second GENOA examination revealing a total cholesterol 5.18 mmol/L or more, triglycerides 1.69 mmol/L or more, or high-density lipoprotein (HDL) 1.04 mmol/L or less.

Laboratory methods

Blood was drawn by venipuncture after an overnight fast of at least 8 hours. Serum glucose, total cholesterol, HDL-cholesterol, and triglyceride concentrations were measured by standard methods on a Hitachi 911 Chemistry Analyzer (Roche Diagnostics, Indianapolis, Indiana, USA). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation when triglycerides were less than 4.5 mmol/L [23]. C-reactive protein (CRP) was measured by a highly sensitive latex particle enhanced immunoturbidimetric assay and expressed in nmol/L.

Statistical analysis

Continuous variables were summarized as medians (25th percentile, 75th percentile). Differences across the 3 groups (nulliparous women, women with a history of normotensive pregnancy, and women with a history of at least one hypertensive pregnancy) were tested using the Kruskal-Wallis test. Pair-wise differences were tested with Wilcoxon rank sum

tests. Categorical variables were summarized as count (percent), and differences across groups were tested with Chi-square tests. We used linear regression models to predict log CRP levels after adjusting for traditional CVD risk factors. We included two indicator variables in the model: one for the presence of at least one pregnancy lasting 6 months, and one for the presence of hypertension in at least one pregnancy. With both indicator variables in the model, the resulting coefficients can be interpreted as contrasting nulliparous and women with a history of normotensive pregnancies, and women with a history of normotensive pregnancies and women with a history of at least one hypertensive pregnancy, respectively. The model included race, age, education, family history of CVD, diabetes, pack-years of smoking, current hypertension, personal history of CHD or stroke, dyslipidemia, use of a statin, and use of hormone replacement therapies as adjustment variables, and was fit with generalized estimating equations to account for the sibling relationships. As CRP levels may be influenced by body mass index (BMI), the model was fit both with and without adjusting for BMI. Due to skewness in the CRP distribution, the log transformed CRP values were used in the model. Additionally, we fit a multiple logistic regression model for elevated CRP, defined as a CRP > 28.6 nmol/L. This model was adjusted for the same variables as the linear model, fit with and without adjusting for BMI, and was fit with generalized estimating equations.

Results

A total of 2463 women were categorized as nulliparous (n=219), women with a history of normotensive pregnancies (n=1839), or women with a history of at least one hypertensive pregnancy (n=405). The median age was 61 years. Baseline clinical characteristics and biochemical parameters for GENOA women with CRP levels measured at the second examination are shown in Table 1.

The 3 categories of women differed significantly in median values for age, BMI, and C-reactive protein; and in the percentages for categories of race, education, hypertension, elevated CRP, family history of hypertension and family history of CHD or stroke (Table 1).

Compared to nulliparous women, women who reported a history of a hypertensive pregnancy had a higher median BMI and CRP, and lower median pack-years among smokers. Women with a history of hypertensive pregnancies also had a lower percentage of dyslipidemia; a higher percentage of non-Hispanic black race, a higher percentage without a high school education and a higher percentage with hypertension, diabetes, elevated CRP, and a positive family history of hypertension compared to nulliparous women.

Compared to women with a history of a normotensive pregnancy, women with a history of a hypertensive pregnancy had a lower median age, a higher median BMI, a higher mean C-reactive protein, and a higher percentage with hypertension, elevated CRP, a family history of hypertension, and a family history of CHD or stroke.

Compared to nulliparous women, women with a history of a normotensive pregnancy were older, had a higher percentage of non-Hispanic black race, and had a higher percentage without a high school education.

In a multiple linear regression model (Table 2), there was no significant difference in mean CRP levels between nulliparous women and those with a history of normotensive pregnancies, after adjusting for age, race, education, family history of CHD or stroke, diabetes, pack-years of smoking, current hypertension, personal history of CHD or stroke, dyslipidemia, use of a statin, use of hormone replacement therapies, and BMI ($p=0.82$). The lack of significant difference remained after removing BMI from the model ($p=0.46$). In contrast, women with a history of a hypertensive pregnancy, compared to those with

normotensive pregnancies, had higher CRP levels, both when BMI was included ($p=0.009$) or removed ($p<0.001$) from the multiple regression model. Of note, a personal history of CHD or stroke was associated with elevated CRP levels, both with and without BMI in the model ($p=0.013$ and $p=0.016$, respectively).

Additionally, similar results were seen using logistic regression for the outcome of elevated CRP, defined as a CRP greater than 28.6 nmol/L (Table 3). After adjusting for the same variables as the linear model, there was no difference in the odds of elevated CRP between nulliparous women and those with a history of normotensive pregnancies either with BMI included ($p=0.99$) or without BMI ($p=0.70$). Women with a history of a hypertensive pregnancy had higher odds of having elevated CRP compared to those with normotensive pregnancies, both with (OR: 1.32, 95% CI: 1.03–1.69, $p=0.031$) and without (OR: 1.53, 95% CI: 1.21–1.94, $p<0.001$) adjusting for BMI. Women on statin therapy, had lower odds of an elevated CRP compared to those not on treatment, either with BMI included (OR: 0.65, 95% CI: 0.51–0.83, $p<0.001$) or without BMI (OR: 0.72, 95% CI: 0.57–0.90, $p=0.004$) in the model. Women taking hormone replacement therapy (HRT) had higher odds of elevated CRP compared to those not on treatment, either with BMI included (OR: 2.41, 95% CI: 1.93–3.00, $p<0.001$) or without BMI (OR: 2.13, 95% CI: 1.73–2.61, $p<0.001$) in the model.

Discussion

Our results indicate that a history of hypertension in pregnancy is associated with elevated CRP levels later in life, independent of traditional CVD risk factors and BMI. In the same cohort of GENOA subjects, we have previously shown that women with a history of a hypertensive pregnancy had a 1.9-fold increased risk of having a subsequent diagnosis of hypertension and a 2.1-fold increased risk of stroke in later life, compared with women with a history of normal blood pressure in pregnancy [8]. Among women in this study, a personal history of CHD or stroke was associated with higher CRP levels. Conceivably, an exaggerated inflammatory response persisting years beyond the pregnancies affected by hypertensive disorders, and as reflected by elevated CRP levels, might have contributed to the increased risk of future CVD events. Our analysis also indicated that CRP levels are lower with the use of a statin and higher with the use of hormone replacement therapies, which is consistent with previous reports [24–26]. Whether the effects of these therapies on CRP correlate with CVD outcomes in patients with a history of hypertensive pregnancy disorders remains to be determined in future studies. Measurement of CRP in these women may aid CVD risk assessment, and may serve as a possible prognostic factor for CVD, or even as a biomarker of the severity of atheromatous disease. We would argue that there may be a role for the measurement of CRP in conjunction with measurement of blood pressure and modifiable CVD risk factors. However, the timing of such screening in the postpartum period has not yet been established.

It has been increasingly recognized that lifelong monitoring of women with a history of hypertensive disorders in pregnancy is needed [3–8]. The inflammatory state may be one of the shared mechanisms leading to hypertensive pregnancy disorders and CVD at different times in a woman's life [27]. CRP levels, which are elevated even in normal human pregnancy [28], are further increased in preeclamptic pregnancies, as early as 13 weeks gestation [29]. Later in life, CRP levels appear to be higher in women than in men [27, 30], and are associated with increased risks for the development of hypertension [31], CHD, ischemic stroke and vascular mortality, although compounded by traditional risk factors. CRP also appears to have a prognostic role for CVD in women [12]. In apparently healthy women 60 years of age or older, measurement of CRP may be useful in selecting patients for statin therapy and may be a reasonable strategy for CVD risk assessment in asymptomatic intermediate-risk women 60 years of age or younger [32]. Evidence from the C Reactive

Protein Coronary Heart Disease Genetics Collaboration has shown that CRP may not have a causal role in CHD, but potentially could be applied as a biomarker of the severity of atheromatous disease, identifying those individuals at risk for CVD [33, 34]. Our study provides evidence that a history of hypertension in pregnancy is associated with elevated CRP levels later in life, suggesting that the inflammatory response may persist years after the hypertensive pregnancies. These data provide the preliminary evidence for future studies of the role of CRP as a marker, and a potential therapeutic target, of an increased future CVD risk in the affected women.

There are a limited number of studies exploring the role of CRP in the post-partum period in women with a history of hypertension in pregnancy. A study looking at 89 women 6 years after a preeclamptic pregnancy, with an average age of 29 years, found no difference in CRP levels when compared to those with a history of normal pregnancies [35]. However, another group reported that CRP was elevated in previously preeclamptic women (n=63) and in women with previous gestational hypertension (n=105), 8 years post-delivery, with an average age of 35 years, but this lost statistical significance when corrected for BMI [36]. Hubel, et al examined 25 postmenopausal women, average age 57 years, 30 years after they had eclampsia, the convulsive variant of the preeclampsia syndrome [37]. They reported elevated CRP levels in women with previous eclampsia when compared to controls, which remained significant when corrected for smoking status, BMI, HRT and current age. Their findings are consistent with ours, with our study extending previous data by providing CRP levels years after the affected pregnancies in a much larger cohort of patients, including nulliparous women, women with preeclampsia, and women with other forms of hypertensive pregnancy disorders. In addition, our findings of higher levels of CRP in women taking hormone replacement therapy support previous reports on this topic [25, 26]. Postmenopausal women using systemic HRT have higher CRP levels; however, transdermal HRT has not been shown to elevate CRP in healthy women [38–42]. Increased plasma levels of CRP and reduced plasma levels of all other markers of inflammation suggest that the increased CRP levels after oral HRT may be related to primary hepatic activation and not secondary to an acute-phase response [43].

Limitations of this study include that CRP was measured after the CVD events, and as a result, we cannot answer the question with our data as to whether CRP is associated with the endpoints of hypertension, CHD and stroke. Another limitation is that the patients recruited were more likely to have a positive family history of hypertension and that they have co-morbidities that may influence CRP levels. However, we made every effort to correct for this by using statistical models in which we adjusted for these variables. A limitation of all studies examining the association of CRP with vascular disease, is the difficulty in concluding whether or not the relationship is causal[44]. Despite these limitations, our data clearly indicate that a history of hypertension in pregnancy is associated with elevated CRP levels later in life.

In conclusion, a history of hypertension in pregnancy is associated with elevated CRP levels later in life, independent of traditional CVD risk factors and BMI. These results set the stage for future population based studies to investigate if elevated CRP in women with a history of hypertension in pregnancy is associated with the endpoints of hypertension, CHD and stroke, and whether CRP has incremental predictive value in CVD risk stratification.

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Abbreviations list

BMI	body mass index
BP	blood pressure
CHD	coronary heart disease
CRP	C-reactive protein
CVD	cardiovascular disease
HDL	high-density lipoprotein
HRT	hormone replacement therapy
hs-CRP	High-sensitivity CRP
LDL	Low-density lipoprotein

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Table 1

All GENOA Subjects with CRP (n=2463)

Variable	N	Nulliparous (N=219)	Normotensive Pregnancy (N=1839)	Hypertensive Pregnancy (N=405)	Overall P-value	Norm. vs. Null. P-value	Hyt. vs. Null. P-value	Hyt. vs. Norm. P-value
Age	2463	57 (48–66)	61 (54–67)	59 (49–65)	<0.001	<0.001	0.51	<0.001
Race, no. (%)	2463				0.001	<0.001	0.001	0.89
Non-Hispanic White		84 (38)	505 (27)	112 (28)				
Hispanic White		70 (32)	544 (30)	115 (28)				
Non-Hispanic Black		65 (30)	790 (43)	178 (44)				
Education, no. (%)	2463				<0.001	<0.001	<0.001	0.13
<= 8 years		41 (19)	460 (25)	88 (22)				
9–11 years		14 (6)	211 (11)	62 (15)				
12 years		52 (24)	547 (30)	116 (29)				
> 12 years		112 (51)	621 (34)	139 (34)				
History of smoking, no. (%)	2463	70 (32)	576 (31)	107 (26)	0.14	0.85	0.14	0.05
Pack-years (among smokers)	751	17 (9–26)	15 (5–30)	11 (4–25)	0.12	0.40	0.035	0.09
Hypertension, no. (%)	2459	155 (71)	1259 (69)	332 (82)	<0.001	0.50	<0.001	<0.001
Diabetes, no. (%)	2462	65 (30)	607 (33)	154 (38)	0.07	0.32	0.037	0.05
BMI	2456	31 (26–38)	31 (27–35)	34 (30–38)	<0.001	0.30	<0.001	<0.001
Dyslipidemia, no. (%)	2463	179 (82)	1433 (78)	300 (74)	0.08	0.20	0.031	0.09
Statins, no. (%)	2463	41 (19)	410 (22)	92 (23)	0.45	0.23	0.24	0.85
HRT, no. (%)	2462	57 (26)	454 (25)	91 (22)	0.54	0.67	0.32	0.34
C Reactive Protein, mmol/L	2463	37 (17–83)	34 (17–69)	47 (23–88)	<0.001	0.23	0.033	<0.001
CRP > 28.6 nmol/L, no. (%)	2463	128 (58)	1035 (56)	274 (68)	<0.001	0.54	0.022	<0.001
Family History of Hypertension, no. (%)	2463	165 (75)	1300 (71)	334 (82)	<0.001	0.15	0.034	<0.001
Family History of CHD or stroke, no. (%)	2463	142 (65)	1092 (59)	278 (69)	0.001	0.12	0.33	<0.001
Personal History of CHD or stroke, no. (%)	2462	23 (11)	195 (11)	54 (13)	0.28	0.96	0.30	0.11

GENOA, Genetic Epidemiology Network of Arteriopathy; Norm, normotensive pregnancy; Null, nulliparous; Hyt, hypertensive pregnancy; HRT, hormone replacement therapy. Values are median (Q1, Q3), unless otherwise noted. The data reported are from the second GENOA study examination visit

Table 2
Multiple linear regression model to predict Log CRP

Subjects: All GENOA subjects with CRP data (2447 in model, 16 missing)

Parameter	β Coefficient*	SE	% Change in CRP**	P value
Normotensive Pregnancy (vs. Nulliparous)	-0.016	0.070	-2%	0.82
Hypertensive Pregnancy (vs. Normotensive)	0.130	0.050	14%	0.009
Race				0.024
Non-Hispanic White	0		0%	
Hispanic	0.178	0.072	19%	0.014
Non-Hispanic Black	0.126	0.054	13%	0.020
Age, per 10 years	-0.006	0.022	-1%	0.77
Education Level				0.20
High School Graduate or GED (12 years)	0		0%	
Less than High School Education (≤ 8 years)	0.052	0.066	5%	0.43
Partial High School Education (9–11 years)	0.086	0.070	9%	0.22
Post High School Education (> 12 years)	-0.053	0.047	-5%	0.26
History of smoking, log (pack-years)	0.063	0.016	6%	<.001
Current Hypertension	0.106	0.045	11%	0.018
Diabetes	0.055	0.047	6%	0.24
Dyslipidemia	0.107	0.047	11%	0.024
Statins	-0.229	0.050	-20%	<.001
Hormone Replacement Therapy	0.435	0.045	55%	<.001
Family History of CHD or Stroke	-0.040	0.042	-4%	0.34
BMI, per 5	0.273	0.015	31%	<.001
Personal History of CHD or Stroke	0.169	0.068	18%	0.013
Intercept	1.452	0.196		<.001

β Coefficient, regression coefficient in model for log CRP; SE, standard error.

* The change in average log (CRP) for a specified unit increase in a continuous variable {age, BMI, log(pack-years)} or the difference in average log (CRP) for one group compared to a reference group for the categorical variables {pregnancy group, race, education, hypertension, diabetes, dyslipidemia, statin usage, HRT, family history of CHD or stroke, personal history of CHD or stroke}.

** The multiplicative effect of a variable on CRP is represented as the % change in CRP. For example, women with a hypertensive pregnancy have an average CRP 14% higher than the average CRP of women with a normotensive pregnancy.

Table 3
Odds ratios and p-values from logistic model of elevated CRP (>28.6 nmol/L)

Subjects: All GENOA subjects with CRP data (2447 in model, 16 missing)

Parameter	OR (95% CI)	Z	P
Normotensive Pregnancy (vs. Nulliparous)	1.00 (0.73, 1.37)	0.01	0.99
Hypertensive Pregnancy (vs. Normotensive)	1.32 (1.03, 1.69)	2.16	0.031
Race			0.18
Non-Hispanic White	1.00		
Hispanic	1.36 (0.98, 1.89)	1.85	0.06
Non-Hispanic Black	1.17 (0.91, 1.50)	1.24	0.22
Age, per 10 years	0.96 (0.87, 1.06)	-0.78	0.44
Education Level			0.34
High School Graduate or GED (12 years)	1.00		
Less than High School Education (<= 8 years)	1.14 (0.85, 1.53)	0.86	0.39
Partial High School Education (9–11 years)	1.13 (0.82, 1.55)	0.73	0.46
Post High School Education (> 12 years)	0.89 (0.72, 1.11)	-1.00	0.32
History of smoking, log (pack-years)	1.11 (1.04, 1.19)	3.05	0.002
Current Hypertension	1.13 (0.91, 1.39)	1.11	0.27
Diabetes	1.06 (0.85, 1.33)	0.52	0.60
Dyslipidemia	1.29 (1.05, 1.59)	2.40	0.016
Statins	0.65 (0.51, 0.83)	-3.51	<.001
Hormone Replacement Therapy	2.41 (1.93, 3.00)	7.80	<.001
Family History of CHD or Stroke	0.93 (0.77, 1.13)	-0.69	0.49
BMI, per 5	1.70 (1.57, 1.84)	12.99	<.001
Personal History of CHD or Stroke	1.29 (0.95, 1.77)	1.61	0.11