The Relationship of a Family History for Hypertension, Myocardial Infarction, or Stroke With Cardiovascular Physiology in Young Women

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Abstract

Cardiovascular disease (CVD) and preeclampsia share several pathophysiologic risk factors. We examined family history (FH) and physiologic status in 60 healthy, nulliparous women to determine the relationship between FH and known risk factors for CVD. Data are presented as mean $\pm$ standard error (SE). Decreased uterine blood flow was observed in women with FH of hypertension (+FH: 21.5 ± 1.7 , no FH: 33.3 ± 9.0 mL/min; $P = .04$). Women reporting an FH of stroke showed increased alpha- and beta-adrenergic response, as measured by Valsalva maneuver (α : FH: 24.7 ± 1.9 , -FH: 18.9 ± 1.1 mm Hg, $P = .02$; β : FH: 22.0 ± 2.1 , -FH: 16.9 ± 1.4 mm Hg; $P = .04$), and increased cardiac output (4.83 ± 0.22 vs 4.31 ± 0.12 L/min; $P = .01$). We identified no significant physiologic associations linked to an FH of myocardial infarction. Our observations show significant differences in physiologic characteristics in women with specific CVD family histories. These data, coupled with known heritable contributions to CVD and preeclampsia, suggest a distinct physiologic phenotype that may link preeclampsia risk with FH of CVD, independent of pregnancy.

Keywords

preeclampsia, hypertension, stroke, family history, plasma volume

Introduction

Cardiovascular disease (CVD) is the fourth leading cause of death worldwide. More than 30% of deaths occurring in the United States in 2008 were attributable to CVD and stroke.¹ While a significant component of this is regularly attributed to lifestyle and environmental influences, a large part is also due to genetic predispositions, as it is clear that individuals with close family members who have had ischemic CVD are at increased risk of developing CVD.²⁻⁵

Women who develop preeclampsia and children born to preeclampsia-complicated pregnancies have increased rates of CVD later in life compared to women who have uncomplicated pregnancies.⁶⁻⁹ While the cause of preeclampsia is unknown, multiple etiologies have been proposed, including placental maladaptation, maternal inflammatory response, underlying predisposition to cardiac disease, an antipaternal immune response, and genetic or epigenetic influences.^{10,11} It is likely that there are multiple etiologies that manifest with the similar clinical presentation of hypertension (HTN) and proteinuria.¹² Cardiovascular characteristics of preeclampsia include reduced plasma volume (PV), increased sympathetic tone, elevated vascular resistance, and peripheral vasoconstriction.¹³⁻¹⁹

Preliminary evidence demonstrates that both low PV and reduced arterial compliance, when identified prior to pregnancy, are associated with the subsequent development of preeclampsia.^{20,21} In addition, increased sympathetic responsiveness and low PV have been linked with CVD, including essential HTN, heart failure, and coronary artery disease.^{22,23}

Preeclampsia and CVD possess several similar strongly heritable physiologic characteristics; our laboratory group contends this suggests a common etiologic origin. In support of this, there are distinct physiologic characteristics that are associated with the development of preeclampsia and CVD.²⁻⁵ Increased pulse pressure (PP) prior to pregnancy and during

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early pregnancy is correlated with the development of preeclampsia, and increased PP has been identified as an independent risk factor for CVD, suggestive of heightened vascular stiffness.^{20,24-27} Decreased PV levels are evident in cases of essential HTN with low PV linked to increased platelet activation, elevated levels of proinflammatory cytokines, and increased sympathetic tone both prior to and during pregnancy, all of which are elements of the preeclamptic pathophysiologic profile.²⁸⁻³⁰

Our research group is focused on examining maternal physiology prior to pregnancy with the goal of understanding how prepregnancy physiology contributes to the pathophysiology of preeclampsia.³¹ Previous work from our laboratory and others suggests certain phenotypic differences exist that predispose some women to the development of gestational hypertensive disorders as well as the development of future cardiac disease.^{32,33} Here, we hypothesized that a family history (FH) for HTN, stroke, or myocardial infarction (MI) would be associated with physiologic characteristics that have been linked to the development of preeclampsia. In this analysis, we have examined, in young healthy nulliparous women, the relationship between an FH of HTN, stroke, or MI with cardiac output (CO), measures of arterial compliance, sympathetic responsiveness, PP, PV, and uterine blood flow (UBF).

Methods

Sixty young, healthy, nonsmoking nulliparous women were recruited via newspapers and poster advertisements. Eligible women had no personal history of HTN, diabetes, autoimmune disease, or other major chronic medical conditions, and were not using hormonal contraceptives. Participants were between the age of 24 and 35 years, with a mean age of 29.6 ± 4.8 years. Participants were of normal body mass index (BMI); mean 22.8 ± 3.7 kg/m², and predominantly caucasian (87%).

Studies were performed in the General Clinical Research Center at the University of Vermont during inpatient evaluation from May 2004 to April 2007. Study evaluation followed 3 days of a 3500-mg sodium-prepared diet to minimize dietary-related hemodynamic variance. Participants were asked to abstain from decongestants and nonsteroidal medications for 48 hours and alcohol and caffeine for 24 hours prior to their evaluation. All studies were performed between 8 AM and 10 AM in the postabsorptive state following an overnight fast. First void urine was used to confirm the nonpregnant status. All women were studied during the follicular phase of the menstrual cycle in order to minimize variability in sex steroid hormones and their influence on UBF, with an average cycle day of 8.7 ± 3.9 . An FH questionnaire evaluated the presence of stroke, MI, and HTN in parents, siblings, and grandparents. Of the 60 participants who were evaluated for physiologic function, 55 provided informative family histories. Data were incomplete for 1 additional participant on FH of MI and HTN, resulting in 54 participants for these analyses. Physiologic evaluations began following 30 minutes of supine rest. For all assessments except Valsalva maneuver, participants remained

in the supine position. The study protocol was approved by both the University of Vermont Institutional Review Board and the University of Vermont General Clinical Research Center Scientific Advisory Committee. All participating women provided written informed consent prior to enrollment.

Hemodynamic Assessment

Both PP and mean arterial pressure (MAP) were measured by continuous noninvasive tonometric radial artery blood pressure monitoring, employing the Colin Pilot 9200 device (San Antonio, Texas) with autostandardization to brachial artery measurements.

The CO was determined by Doppler echocardiographic examination. Forward stroke volume across the aortic valve was calculated as the product of the left ventricular outflow area and the outflow tract velocity time integral as assessed by pulsed Doppler using previously described methods.³⁴ 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. The CO is expressed as liter/minute after the integration of stroke volume with pulse rate.

The UBF was estimated using color Doppler ultrasound with an 8.0-MHz transvaginal transducer employing a Vivid 7 General Electric ultrasound unit (Milwaukee, Wisconsin). Uterine artery measurements were obtained lateral to the cervix at the level of the internal os. Vessel diameter was measured between the inner surfaces of the vessel walls during real-time power color Doppler imaging as previously described.³⁴ Uterine index (UI) was calculated as UBF divided by CO. This calculation was used to evaluate the differences between groups in allocation of systemic blood flow to the uterine arteries.

Alpha- and beta-adrenergic responsiveness were estimated based on temporally sequenced blood pressure responses to Valsalva maneuver.³⁵ Participants created a forced expiration for 20 seconds against a nonfixed low flow resistance to a pressure of 60 mm Hg 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 [PIIL]) response and reflects baroreceptor activity mediated by vascular alpha-adrenergic receptors. The calculated difference between baseline MAP and the top of phase IV (PIV) represents the PIV measurement and reflects beta-adrenergic activity.³⁵

The PV was calculated using the Evans Blue Dye method, as previously described.³⁶ An 18-gauge intravenous saline lock was placed in the antecubital vein for baseline blood draw and administration of Evans blue dye and subsequent blood draws. The PV was reported in total milliliter and corrected for BMI.

Data Analysis

Participants with and without a FH of HTN, stroke, and MI were assessed and compared on the following physiological measures: BMI, MAP, PP, CO, UBF, UI, PV corrected for BMI

Table 1. Comparison of Physiologic Characteristics in Those With and Without Family History for Hypertension.^a

Physiologic Variable	No Family History of Hypertension (−FH), n = 13 Mean ± SE	History of Hypertension (+FH), n = 42 Mean ± SE	P Value
Age, years	28.21 ± 1.18	30.19 ± 0.75	.21
BMI, kg/m ²	24.31 ± 1.41	22.41 ± 0.47	.10
Cardiac output, L/min	4.73 ± 0.20	4.48 ± 0.13	.36
Uterine blood flow, mL/min	33.33 ± 8.97	21.46 ± 1.65	.04
Uterine index, %	6.80 ± 1.47	4.91 ± 0.39	.08
PIIL, alpha-adrenergic response, mm Hg	21.46 ± 1.51	20.55 ± 1.36	.72
PIV, beta-adrenergic response, mm Hg	16.31 ± 3.02	19.45 ± 1.26	.26
Mean arterial pressure, mm Hg	72.46 ± 3.99	78.87 ± 1.60	.08
Pulse pressure, mm Hg	45.77 ± 1.02	48.29 ± 1.49	.34
Plasma volume, corrected for BMI, mL/kg/m ²	131.93 ± 4.61	127.26 ± 2.61	.39

Abbreviations: FH, family history; BMI, body mass index; PIIL, late phase II; PIV, phase IV; SE, standard error.

^aMean, standard error, and P values comparing physiologic characteristics in those with and without the family history for hypertension.

(PV/BMI), PIIL (alpha-adrenergic activity), and PIV (beta-adrenergic activity). Initially, separate univariate analyses were performed comparing participants with and without an FH of HTN, stroke, and MI using *t* tests. Because many participants had FHs of multiple outcomes of interest, a linear model was subsequently constructed to estimate the independent contribution of each of the 3 factors through the use of indicator variables. The intercept in the linear model represents the estimated least square mean for participants with no FH of any of the factors and least square means for each factor can be computed by adding the appropriate coefficient to the intercept.

When appropriate, descriptive statistics are reported for the subset of participants who had multigenerational FH (first and second degree), as small sample sizes precluded inferential analyses.

All statistical analyses were performed using SAS Statistical Software Version 9.3 (SAS Institute, Cary, North Carolina). Statistical significance was determined using *P* = .05.

Results

Hypertension

Mean age, BMI, CO, PP, PIIL, or PIV did not significantly differ between women with and without an FH of HTN (Table 1). Women reporting FH of HTN had decreased UBF in comparison to those without (−FH: 33.3 ± 9.0 vs +FH: 21.5 ± 1.7 mL/min; *P* = .04). This result was consistent with a trend seen in UI (UBF/CO). Women with an FH had a trend toward a lower UI in comparison to women with no FH of HTN (−FH: 6.8% ± 1.5% vs +FH: 4.9% ± 0.4%; *P* = .08). There was also a trend toward increased MAP in participants with FH of HTN (−FH: 72.5 ± 4.0 mm Hg vs +FH: 78.9 ± 1.6 mm Hg; *P* = .08).

While women with FH of HTN did not have a significantly lower PV/BMI than those without a history of HTN (−FH: 131.2 ± 4.5 mL/kg vs +FH: 128.4 ± 2.9 mL/kg; *P* = .4), it is interesting to note that in the 13 participants with multigenerational FH of HTN, a decreased PV/BMI was suggested (mean 121.0 ± 4.6 mL/kg).

Analyses adjusting for other risk factors failed to demonstrate significant differences in physiological characteristics specifically attributable to an FH of HTN. The estimated decrease in mean UBF observed univariately was similar in magnitude but did not achieve statistical significance (Table 2; −FH: 35.2 ± 5.5 vs +FH HTN: 24.3 ± 4.5 mL/min; *P* = .09).

Stroke

There were no significant differences in mean age, BMI, UBF, UI, MAP, PP, or PV/BMI, in those with and without an FH of stroke (Table 3). Mean CO was significantly increased in women reporting FH of stroke compared to those with no FH of stroke (−FH: 4.31 ± 0.12 L/min vs +FH: 4.83 ± 0.22; *P* = .01). Participants who reported an FH of stroke had a significantly higher pII late (alpha-adrenergic response), as assessed by Valsalva, than those without a history (Table 3; −FH: 18.9 ± 1.2 mm Hg vs +FH: 24.7 ± 1.9; *P* = .02). PIV sympathetic response, reflective of beta-adrenergic response, was observed to be increased in participants with relations who had an FH of stroke as compared to those without FH (−FH: 16.9 ± 1.4 vs +FH: 22.0 ± 2.1 mm Hg; *P* = .04).

The results of multivariate analyses adjusting for other risk factors closely paralleled univariate results, with similar magnitude of estimated differences among analyses. Sympathetic tone, both PIIL and PIV, was higher in women with an FH of stroke (Table 2; PIIL: −FH: 19.5 ± 2.32 mm Hg vs +FH: 24.8 ± 2.6; *P* = .02, and PIV: −FH: 13.8 ± 2.5 mm Hg vs +FH: 18.5 ± 2.9; *P* = .06). Additionally, average CO was significantly increased in women with an FH of stroke, in comparison to those with no FH (−FH: 4.4 ± 0.2 L/min vs +FH: 5.0 ± 0.3; *P* = .01).

Myocardial Infarction

There were no significant differences in participants with an FH of MI in comparison to those with no FH. However, trends were observed in UI, beta-adrenergic response, and MAP (Table 4). Women with an FH of MI demonstrated a trend

Table 2. Estimates of Physiologic Characteristics in Participants With No Family History for Hypertension, Myocardial Infarction, or Stroke Compared to Those Reporting Family Histories for Each Cardiovascular Diagnosis.^a

Physiologic Variable	No Family History	Hypertension Only	P Value	Stroke Only	P Value	Myocardial Infarction Only	P Value
Age, years	28.67 ± 1.46	30.71 ± 1.21	.22	27.91 ± 1.46	.58	28.35 ± 1.86	.82
BMI, kg/m ²	23.71 ± 1.10	21.77 ± 0.91	.12	25.03 ± 0.24	.22	24.09 ± 1.40	.73
Cardiac output, L/min	4.44 ± 0.24	4.11 ± 0.20	.22	5.03 ± 0.27	.01	4.71 ± 0.31	.26
Uterine blood flow, mL/min	35.20 ± 5.49	24.33 ± 4.56	.09	32.74 ± 6.21	.64	31.18 ± 7.01	.16
Uterine index, %	7.39 ± 1.00	5.81 ± 0.84	.17	6.53 ± 1.14	.38	6.27 ± 1.28	.26
PIIL, alpha-adrenergic response, mm Hg	19.46 ± 2.32	18.84 ± 1.99	.82	24.83 ± 2.62	.02	19.19 ± 2.97	.91
PIV, beta-adrenergic response, mm Hg	13.77 ± 2.54	15.80 ± 2.18	.49	18.52 ± 2.87	.06	16.85 ± 3.25	.22
Mean arterial pressure, mm Hg	70.30 ± 3.36	75.50 ± 3.03	.19	74.13 ± 3.84	.25	73.30 ± 4.40	.39
Pulse pressure, mm Hg	45.75 ± 2.54	48.84 ± 2.29	.30	46.50 ± 2.90	.76	44.58 ± 3.32	.66
Plasma volume, corrected for BMI, mL/kg/m ²	132.77 ± 5.16	127.37 ± 4.28	.35	129.11 ± 5.84	.62	135.26 ± 6.58	.46

Abbreviation: BMI, body mass index; PIIL, PIIL, late phase II; PIV, phase IV; SEM, standard error of mean.

^aTabled values represent least square means, SEM, and *P* values derived from linear regression model.

Table 3. Comparison of Physiologic Characteristics in Those With and Without Family History for Stroke.^a

Physiologic Variable	No Family History of Stroke (–FH), n = 35 Mean ± SE	History of Stroke (+FH), n = 19 Mean ± SE	P Value
Age, years	30.09 ± 0.90	29.44 ± 0.83	.53
BMI, kg/m ²	22.40 ± 0.57	23.78 ± 0.95	.17
Cardiac output, L/min	4.31 ± 0.12	4.83 ± 0.22	.01
Uterine Blood Flow, mL/min	24.86 ± 3.74	22.68 ± 2.13	.62
Uterine index, %	5.63 ± 0.67	4.82 ± 0.48	.32
PIIL, alpha-adrenergic Response, mm Hg	18.85 ± 1.21	24.72 ± 1.92	.02
PIV, beta-adrenergic response, mm Hg	16.85 ± 1.39	22.00 ± 2.10	.04
Mean arterial pressure, mm Hg	75.79 ± 1.83	80.24 ± 2.99	.22
Pulse pressure, mm Hg	47.49 ± 1.41	47.94 ± 2.04	.85
Plasma volume, corrected for BMI, mL/kg/m ²	129.81 ± 2.74	126.83 ± 4.15	.52

Abbreviations: FH, family history; BMI, body mass index; PIIL, late phase II; PIV, phase IV; SE, standard error.

^aMean, standard error, and *P* values comparing physiologic characteristics in those with and without family history for stroke.

toward decreased UI in comparison to those with no FH (–FH: 6.2% ± 0.9% vs +FH: 4.5% ± 0.4%; *P* = .07). Beta-adrenergic response trended higher in women with an FH of MI (–FH: 16.3 ± 2.0 vs +FH: 20.6 ± 1.4; *P* = .08).

There were no significant differences in physiologic characteristics attributable to reporting an FH of MI in analyses adjusted for other familial risk factors, though again the estimated differences between groups remained consistent with those found univariately (Table 2). Of note, the vast majority (27 of 29) of those reporting a positive history for MI also reported a positive history for an alternative cardiovascular outcome, with 11 of 29 reporting FHs for all 2 evaluated outcomes.

Discussion

Women reporting an FH of HTN, stroke, or MI were found to have different physiologic profiles dependent on their histories. Women with an FH of stroke had increased CO and increased alpha- and beta-adrenergic response. Women with an FH of HTN presented with decreased UBF, and women with an FH

of MI did not show any differences from women without. These findings add evidence to the importance of FH in evaluating cardiovascular risk profiles. Of interest, CVD and preeclampsia share several physiologic characteristics and women who develop preeclampsia are at an increased risk of developing CVD later in life.^{6,37} There is strong evidence that preeclampsia is familial and is associated with increased long-term risk for the subsequent development of HTN and ischemic CVD outside pregnancy.³⁸ Women who have been diagnosed with preeclampsia during pregnancy have an increased risk of nonpregnancy-associated stroke, both in the first year postpartum and during their later years, as well as an increased risk of death from CVD.^{37,39,40} It has been reported that an FH of HTN increases an individual's likelihood of developing HTN themselves by up to 400 times.⁴¹ In addition, FH of HTN has been suggested to increase preeclampsia risk in women.⁴² There is a growing body of evidence highlighting a relationship, either causal or confounding, between hypertensive disorders during pregnancy and subsequent risk of CVD.^{6,13,37,43} There are 2 arguments, the first that preeclampsia results in

Table 4. Comparison of Physiologic Characteristics in Those With and Without Family History for Myocardial Infarction (MI).^a

Physiologic Variable	No Family History of Myocardial Infarction (–FH), n = 25	History of Myocardial Infarction (+FH), n = 29	P Value
	Mean ± SE	Mean ± SE	
Age, years	29.68 ± 0.89	29.86 ± .95	.89
BMI, kg/m ²	22.92 ± 0.65	22.90 ± 0.76	.98
Cardiac output, L/min	4.41 ± 0.15	4.65 ± 0.17	.29
Uterine blood flow, mL/min	27.99 ± 5.05	20.42 ± 1.65	.14
Uterine index, %	6.20 ± 0.89	4.50 ± 0.36	.07
PIIL, alpha-adrenergic response, mm Hg	20.67 ± 1.51	20.86 ± 1.56	.93
PIV, beta-adrenergic response, mm Hg	16.33 ± 2.01	20.62 ± 1.37	.08
Mean arterial pressure, mm Hg	74.18 ± 2.32	79.55 ± 2.11	.10
Pulse pressure, mm Hg	47.64 ± 1.43	47.66 ± 1.73	.99
Plasma volume, corrected for BMI, mL/kg/m ²	128.50 ± 3.19	128.90 ± 3.30	.93

Abbreviation: BMI, body mass index; PIIL, PIIL, late phase II; PIV, phase IV; FH, family history; SE, standard error; MI, myocardial infarction.

^aMean, standard error, and P values comparing physiologic characteristics in those with and without family history for MI.

lifelong cardiac changes that increase the risk of future events. The second hypothesis, which our laboratory explores, attempts to explain preeclampsia primarily as a hypertensive event of pregnancy, brought on by a predisposing phenotype.

Of the 55 included participants, 42 reported an FH significant for HTN, 19 reported that of stroke, and 29 reported an FH of MI. Our analyses attempted to investigate the individual contribution of each to cardiovascular physiologic mechanisms, although the interplay between multiple risk factors does not allow for a clean analysis. Most strikingly, 27 of the 29 participants reporting an FH of MI also report histories of either HTN or stroke, 11 of which report histories of all 3. Hypertension, stroke, and MI have related but differing etiologies, and while HTN is traditionally a risk factor for both stroke and MI, the specific mechanism has not been fully explained.⁴⁴ Alternately, a history of stroke does not increase the risk of MI or vice versa. Each cardiovascular event appears to develop due to an independent, yet related mechanism. For this reason, we examined the association between physiologic characteristics in women with HTN, stroke, and MI both independently of one another as well as comparing those with specific family histories to those where there was no FH of any of these disorders.

When comparing women with no FH of HTN, stroke, or MI with those experiencing only a singular FH, our findings were limited by small sample sizes, and we were only able to detect a singular statistically significant difference between groups, that of increased CO in women with an FH of stroke. Despite our limited statistical findings, it is worthwhile to note that the direction and magnitude of the estimated differences for all physiologic markers were consistent with the univariate findings. In our analysis, nulliparous women with a positive FH of HTN, MI, or stroke possess physiologic differences in markers typically understood to establish the risk for the development of ischemic CVD independent of pregnancy. These physiologic markers become more evident in those with multigenerational family histories. Physiologically, CVD risk factors including reduced PV, increased PP, and increased

sympathetic response have been identified as clinical precursors to both CVD and preeclampsia, and there is evidence these factors are altered prior to pregnancy in women who subsequently develop preeclampsia.^{20,45,46} Higher values in MAP and sympathetic tone, as well as decreased PV/BMI in participants with positive FH of HTN, stroke, or MI, suggest these physiologic factors have a familial component that contributes to cardiovascular function, even prior to onset of clinical disease. In addition to the aforementioned physiologic risk factors, our study measured a significantly lower UBF in women with an FH of HTN. Diameter of uterine vessels was comparable across all groups. Reduced UBF, both prior to and during pregnancy, has been linked to the development of intrauterine growth restriction.^{47–49} Prepregnancy UBF is not routinely evaluated, and studies tracking volumetric UBF expansion in early pregnancy are limited. There are conflicting reports of the hemodynamic effects of estradiol and progesterone, although there is a well-established cyclical effect seen, with higher levels of UBF seen throughout the follicular and preovulatory phases of the menstrual cycle, and reduced levels during the early follicular phase.^{50,51} For the sake of continuity across participants, all participants were evaluated in the follicular phase. The UBF has been reported to increase by 10× from prepregnancy to early pregnancy, and data suggest that differences in UBF during early pregnancy may reflect differences present prior to pregnancy.⁵² In addition, UBF can be significantly decreased in women both who develop gestational HTN or preeclampsia, and who deliver preterm compared to those who deliver near term.⁵³

Several of the measured physiologic parameters, in particular elevated CO, increased sympathetic tone, and low PV/BMI (when present in multigenerational family histories) that differ in nulliparous women with an FH of CVD, have also been recognized as contributing to predisposition to preeclampsia.^{21,54,55} We suggest that these prepregnancy phenotypes may contribute to both a physiologic predisposition to preeclampsia and a long-term risk for CVD. Observations of CO in early pregnancy linked increased CO with the subsequent

development of preeclampsia, and low levels of prepregnancy PV have been linked to the risk for recurrent and subsequent preeclampsia.^{14,21,54} While the youthfulness of the study population likely contributed to the low number of women reporting FHs involving both first- and second-generation relations who have had MI or stroke, the presence of FH of a first-degree cardiovascular event in our young population is generally indicative of early-onset CVD. Early- versus late-onset CVD in relatives is an important factor to consider in taking FH. Many studies have found that the risk for developing CVD is significantly increased when family members have experienced early-onset disease as opposed to late onset.^{4,56-61} It is well established that early-onset CVD disease is often more severe and is associated with increased risk of preeclampsia.^{4,62} Conversely, the timing and severity of hypertensive disease during pregnancy are also predictive of early-onset CVD, with women who develop severe preeclampsia early in pregnancy having the highest incidence of early-onset CVD.⁶³ Women who develop severe preeclampsia, especially early-onset, have a higher rate of deaths attributable to CVD as well as an increased risk of having family members who have had early-onset CVD of any type.^{15,21,54,62}

Although this study was small, specifically preventing us from exploring the relationship and statistical significance of first- and second-generational FH for HTN, MI, and stroke, we were able to identify several known physiologic clinical precursors to both preeclampsia and ischemic CVD, supporting the hypothesis that there is a nonpregnancy phenotype that exists in young women who have an FH of these cardiovascular events. This phenotype likely contributes to the “pregnancy as a stress-test” hypothesis, whereby preeclampsia unmasks preexisting physiologic characteristics that predispose to preeclampsia and future CVD risk.^{31,43} Considering the relatively small sample size, it is possible that additional relationships may exist but the study was underpowered to detect. Further limitations of our study include the potential for recall bias or misinformation from our participants regarding the incidence of HTN, MI, or stroke in their family members, and a lack of data regarding FH of preeclampsia. Also, as we were interested in studying the cardiovascular physiology of healthy nulligravid women, we excluded those with obesity. Consequently by excluding those with higher BMI values, the potential for selection bias may have limited our results as BMI is a well-established risk factor for both CVD and preeclampsia.

Without birth outcome data on study participants, and assuming a rate of 5% to 8% of pregnancies develop preeclampsia, it is impossible to predict which small subset of our population would likely develop preeclampsia. Risk factors commonly overestimate projected risk in order to have a higher positive projected risk. Clearly, not all participants who are at risk of developing HTN, stroke, or MI will experience these cardiovascular events. The Norwegian HUNT study revealed that up to 83.7% of the population exhibited a positive profile of at least 2 risk factors for CVD, and 98% of the population exhibited at least 1 risk factor.⁶⁴ Similarly, the Framingham

score and European SCORE models both profoundly overestimate the risk of CVD.⁶⁵ However, despite the potential for overestimation of risk, FH remains a highly significant predictor of HTN, stroke, and MI risk in siblings, offspring, and grandchildren of those who have experienced CVD events, particularly when correlated to physiologic profiles. Similarly, we argue that the risk of preeclampsia development can likewise be estimated through a combination of familial and phenotypic physiologic characteristics.

In summary, women reporting an FH of HTN had decreased UBF, and those reporting an FH of stroke were found to have increased CO, and increased alpha- and beta-adrenergic response in comparison to women without FHs of these cardiovascular events. This study has potential implications for both obstetrical and cardiovascular health. Before the onset of disease, it may be possible to identify women at risk of developing preeclampsia or CVD based on physiologic assessments of their cardiovascular phenotype or strongly associated markers. The ability to enhance the identification of women at high cardiovascular risk could facilitate early intervention for clinically manifest pregnancy-related risks and long-term cardiovascular health risks.

Authors' Notes

The research was performed at the University of Vermont, Burlington, Vermont, USA.

Declaration of Conflicting Interests

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References

1. Minino AM, Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2008. *Natl Vital Stat Rep*. 2011;59(10):1-126.
2. Banerjee A, Silver LE, Heneghan C, et al. Sex-specific familial clustering of myocardial infarction in patients with acute coronary syndromes. *Circ Cardiovasc Genet*. 2009;2(2):98-105.
3. Touze E, Rothwell PM. Sex differences in heritability of ischemic stroke: a systematic review and meta-analysis. *Stroke*. 2008; 39(1):16-23.
4. Nora JJ, Lortscher RH, Spangler RD, Nora AH, Kimberling WJ. Genetic—epidemiologic study of early-onset ischemic heart disease. *Circulation*. 1980;61(3):503-508.
5. Lindgren A, Lovkvist H, Hallstrom B, et al. Prevalence of stroke and vascular risk factors among first-degree relatives of stroke patients and control subjects. A prospective consecutive study. *Cerebrovasc Dis*. 2005;20(5):381-387.

6. Anderson CM. Preeclampsia: exposing future cardiovascular risk in mothers and their children. *J Obstet Gynecol Neonatal Nurs*. 2007;36(1):3-8.
7. Jonsdottir LS, Arngrimsson R, Geirsson RT, Sigvaldason H, Sigfusson N. Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. *Acta Obstet Gynecol Scand*. 1995;74(10):772-776.
8. Wikstrom AK, Haglund B, Olovsson M, Lindeberg SN. The risk of maternal ischaemic heart disease after gestational hypertensive disease. *BJOG*. 2005;112(11):1486-1491.
9. Hannaford P, Ferry S, Hirsch S. Cardiovascular sequelae of toxemia of pregnancy. *Heart*. 1997;77(2):154-158.
10. Bushnell C, Chireau M. Preeclampsia and stroke: risks during and after pregnancy. *Stroke Res Treat*. 2011;2011:858134.
11. Walker JJ. Pre-eclampsia. *Lancet*. 2000;356(9237):1260-1265.
12. Roes EM, Sieben R, Raijmakers MT, Peters WH, Steegers EA. Severe preeclampsia is associated with a positive family history of hypertension and hypercholesterolemia. *Hypertens Pregnancy*. 2005;24(3):259-271.
13. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007;335(7627):974.
14. Bosio PM, McKenna PJ, Conroy R, O'Herlihy C. Maternal central hemodynamics in hypertensive disorders of pregnancy. *Obstet Gynecol*. 1999;94(6):978-984.
15. Lewinsky RM, Riskin-Mashiah S. Autonomic imbalance in preeclampsia: evidence for increased sympathetic tone in response to the supine-pressor test. *Obstet Gynecol*. 1998;91(6):935-939.
16. Poppas A, Shroff SG, Korcarz CE, et al. Serial assessment of the cardiovascular system in normal pregnancy. Role of arterial compliance and pulsatile arterial load. *Circulation*. 1997;95(10):2407-2415.
17. Robb AO, Din JN, Mills NL, et al. The influence of the menstrual cycle, normal pregnancy and pre-eclampsia on platelet activation. *Thromb Haemost*. 2009;103(2):372-378.
18. Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia—a state of sympathetic overactivity. *N Engl J Med*. 1996;335(20):1480-1485.
19. Tiihonen KM, Koobi T, Uotila JT. Arterial stiffness in preeclamptic and chronic hypertensive pregnancies. *Eur J Obstet Gynecol Reprod Biol*. 2006;128(1-2):180-186.
20. Hale S, Choate M, Schonberg A, Shapiro R, Badger G, Bernstein IM. Pulse pressure and arterial compliance prior to pregnancy and the development of complicated hypertension during pregnancy. *Reprod Sci*. 2010;17(9):871-877.
21. Aardenburg R, Spaanderman ME, van Eijndhoven HW, de Leeuw PW, Peeters LL. A low plasma volume in formerly preeclamptic women predisposes to the recurrence of hypertensive complications in the next pregnancy. *J Soc Gynecol Investig*. 2006;13(8):598-603.
22. Charkoudian N, Rabbitts JA. Sympathetic neural mechanisms in human cardiovascular health and disease. *Mayo Clin Proc*. 2009;84(9):822-830.
23. Fisher JP, Young CN, Fadel PJ. Central sympathetic overactivity: maladies and mechanisms. *Auton Neurosci*. 2009;148(1-2):5-15.
24. Fontes ML, Aronson S, Mathew JP, et al. Pulse pressure and risk of adverse outcome in coronary bypass surgery. *Anesth Analg*. 2008;107(4):1122-1129.
25. Safar ME. New problems raised by increased pulse pressure. *Eur Heart J*. 2005;26(20):2081-2082.
26. de Simone G, Chinali M. High pulse pressure as a marker of preclinical cardiovascular disease. *Future Cardiol*. 2006;2(2):165-168.
27. Safar ME. Systolic blood pressure, pulse pressure and arterial stiffness as cardiovascular risk factors. *Curr Opin Nephrol Hypertens*. 2001;10(2):257-261.
28. Reslan OM, Khalil RA. Molecular and vascular targets in the pathogenesis and management of the hypertension associated with preeclampsia. *Cardiovasc Hematol Agents Med Chem*. 2011;8(4):204-226.
29. Tarazi RC, Frohlich ED, Dustan HP. Plasma volume in men with essential hypertension. *N Engl J Med*. 1968;278(14):762-765.
30. Tibblin G, Bergentz SE, Bjure J, Wilhelmsen L. Hematocrit, plasma protein, plasma volume, and viscosity in early hypertensive disease. *Am Heart J*. 1966;72(2):165-176.
31. Bernstein IM, Meyer MC, Osol G, Ward K. Intolerance to volume expansion: a theorized mechanism for the development of preeclampsia. *Obstet Gynecol*. 1998;92(2):306-308.
32. Bernstein IM, Ziegler W, Stirewalt WS, Brumsted J, Ward K. Angiotensinogen genotype and plasma volume in nulligravid women. *Obstet Gynecol*. 1998;92(2):171-173.
33. Ness RB, Markovic N, Bass D, Harger G, Roberts JM. Family history of hypertension, heart disease, and stroke among women who develop hypertension in pregnancy. *Obstet Gynecol*. 2003;102(6):1366-1371.
34. Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. *Circulation*. 1984;70(3):425-431.
35. Denq JC, O'Brien PC, Low PA. Normative data on phases of the Valsalva maneuver. *J Clin Neurophysiol*. 1998;15(6):535-540.
36. Bernstein IM, Damron D, Schonberg AL, Shapiro R. The relationship of plasma volume, sympathetic tone, and proinflammatory cytokines in young healthy nonpregnant women. *Reprod Sci*. 2009;16(10):980-985.
37. Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. *Hypertension*. 2011;56(1):166-171.
38. Chesley LC, Annitto JE, Cosgrove RA. The familial factor in toxemia of pregnancy. *Obstet Gynecol*. 1968;32(3):303-311.
39. Brown DW, Dueker N, Jamieson DJ, et al. Preeclampsia and the risk of ischemic stroke among young women: results from the Stroke Prevention in Young Women Study. *Stroke*. 2006;37(4):1055-1059.
40. Tang CH, Wu CS, Lee TH, et al. Preeclampsia-eclampsia and the risk of stroke among peripartum in Taiwan. *Stroke*. 2009;40(4):1162-1168.
41. van der Sande MA, Walraven GE, Milligan PJ, et al. Family history: an opportunity for early interventions and improved control

- of hypertension, obesity and diabetes. *Bull World Health Organ.* 2001;79(4):321-328.
42. Qiu C, Williams MA, Leisenring WM, et al. Family history of hypertension and type 2 diabetes in relation to preeclampsia risk. *Hypertension.* 2003;41(3):408-413.
 43. Craici I, Wagner S, Garovic VD. Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test? *Ther Adv Cardiovasc Dis.* 2008;2(4):249-259.
 44. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation.* 2006;113(19):2363-2372.
 45. Romundstad PR, Magnussen EB, Smith GD, Vatten LJ. Hypertension in pregnancy and later cardiovascular risk: common antecedents? *Circulation.* 2010;122(6):579-584.
 46. Scholten RR, Hopman MT, Sweep FC, et al. Co-occurrence of cardiovascular and prothrombotic risk factors in women with a history of preeclampsia. *Obstet Gynecol.* 2013;121(1):97-105.
 47. Ferrazzi E, Rigano S, Padoan A, Boito S, Pennati G, Galan HL. Uterine artery blood flow volume in pregnant women with an abnormal pulsatility index of the uterine arteries delivering normal or intrauterine growth restricted newborns. *Placenta.* 2011;32(7):487-492.
 48. Konje JC, Howarth ES, Kaufmann P, Taylor DJ. Longitudinal quantification of uterine artery blood volume flow changes during gestation in pregnancies complicated by intrauterine growth restriction. *BJOG.* 2003;110(3):301-305.
 49. Scholten RR, Sep S, Peeters L, Hopman MT, Lotgering FK, Spaanderman ME. Prepregnancy low-plasma volume and predisposition to preeclampsia and fetal growth restriction. *Obstet Gynecol.* 2011;117(5):1085-1093.
 50. Steer CV, Campbell S, Pampiglione JS, Kingsland CR, Mason BA, Collins WP. Transvaginal colour flow imaging of the uterine arteries during the ovarian and menstrual cycles. *Hum Reprod.* 1990;5(4):391-395.
 51. Ziegler WF, Bernstein I, Badger G, Leavitt T, Cerrero ML. Regional hemodynamic adaptation during the menstrual cycle. *Obstet Gynecol.* 1999;94(5 pt 1):695-699.
 52. Hale SA, Schonberg A, Badger GJ, Bernstein IM. Relationship between prepregnancy and early pregnancy uterine blood flow and resistance index. *Reprod Sci.* 2009;16(11):1091-1096.
 53. Browne VA, Toledo-Jaldin L, Davila RD, et al. High-end arteriolar resistance limits uterine artery blood flow and restricts fetal growth in preeclampsia and gestational hypertension at high altitude. *Am J Physiol Regul Integr Comp Physiol.* 2011;300(5):R1221-R1229.
 54. Easterling TR, Benedetti TJ, Schmucker BC, Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. *Obstet Gynecol.* 1990;76(6):1061-1069.
 55. Gyselaers W, Mullens W, Tomsin K, Mesens T, Peeters L. Role of dysfunctional maternal venous hemodynamics in the pathophysiology of pre-eclampsia: a review. *Ultrasound Obstet Gynecol.* 2011;38(2):123-129.
 56. Barrett-Connor E, Khaw K. Family history of heart attack as an independent predictor of death due to cardiovascular disease. *Circulation.* 1984;69(6):1065-1069.
 57. Friedlander Y, Kark JD, Stein Y. Family history of myocardial infarction as an independent risk factor for coronary heart disease. *Br Heart J.* 1985;53(4):382-387.
 58. Hoseini K, Sadeghian S, Mahmoudian M, Hamidian R, Abbasi A. Family history of cardiovascular disease as a risk factor for coronary artery disease in adult offspring. *Monaldi Arch Chest Dis.* 2008;70(2):84-87.
 59. Jousilahti P, Rastenyte D, Tuomilehto J, Sarti C, Vartiainen E. Parental history of cardiovascular disease and risk of stroke. A prospective follow-up of 14371 middle-aged men and women in Finland. *Stroke.* 1997;28(7):1361-1366.
 60. Seshadri S, Beiser A, Pikula A, et al. Parental occurrence of stroke and risk of stroke in their children: the Framingham study. *Circulation.* 2010;121(11):1304-1312.
 61. Shea S, Ottman R, Gabrieli C, Stein Z, Nichols A. Family history as an independent risk factor for coronary artery disease. *J Am Coll Cardiol.* 1984;4(4):793-801.
 62. Rigo J Jr, Boze T, Derzsy Z, et al. Family history of early-onset cardiovascular disorders is associated with a higher risk of severe preeclampsia. *Eur J Obstet Gynecol Reprod Biol.* 2006;128(1-2):148-151.
 63. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *Lancet.* 2005;366(9499):1797-1803.
 64. Petursson H, Getz L, Sigurdsson JA, Hetlevik I. Can individuals with a significant risk for cardiovascular disease be adequately identified by combination of several risk factors? Modelling study based on the Norwegian HUNT 2 population. *J Eval Clin Pract.* 2009;15(1):103-109.
 65. Qureshi N, Armstrong S, Dhiman P, et al. Effect of adding systematic family history enquiry to cardiovascular disease risk assessment in primary care: a matched-pair, cluster randomized trial. *Ann Intern Med.* 2012;156(4):253-262.