ORIGINAL RESEARCH

Life-Course Reproductive History and Cardiovascular Risk Profile in Late Mid-Life: The CARDIA Study

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BACKGROUND: Reproductive events, that is, a preterm birth (PTB), small-for-gestational-age infant (SGA), and vasomotor symptoms of menopause, are associated with subclinical atherosclerotic cardiovascular disease (ASCVD). We evaluated whether women with a past PTB and/or SGA (henceforth PTB/SGA) were more likely to have severe vasomotor symptoms of menopause and whether the estimated 10-year ASCVD risk was higher in women with PTB/SGA and vasomotor exposures.

METHODS AND RESULTS: We assigned 1866 women (mean age=55±1 years) in the CARDIA (Coronary Artery Risk Development in Young Adults) study to the following categories of reproductive exposures: none, PTB/SGA only, vasomotor symptoms only, or both PTB/SGA and vasomotor symptoms. We used Kruskal-Wallis tests to evaluate the differences in pooled cohort equation ASCVD risk scores by category and linear regression to evaluate the associations of categories with ASCVD risk scores adjusted for study center, body mass index, education, current hormone replacement therapy use, parity, and hysterectomy. Women with PTB/SGA were more likely to have severe vasomotor symptoms, 36% versus 30%, $P<0.02$. ASCVD risk score was higher in women with both PTB/SGA and vasomotor symptoms (4.6%; 95% CI, 4.1%–5.1%) versus women with no exposures (3.3%; 95% CI, 2.9%–3.7%) or vasomotor symptoms only (3.8%; 95% CI, 3.5%–4.0%). ASCVD risk score was higher in women PTB/SGA (4.8%; 95% CI, 3.6%–5.9%) versus no exposures. PTB/SGA and vasomotor symptoms was associated with ASCVD risk score in white women versus no exposures ($\beta=0.40$; 95% CI, 0.02–0.78).

CONCLUSIONS: Women with prior PTB/SGA were more likely to have severe vasomotor symptoms of menopause. Reproductive exposures were associated with an estimated 10-year ASCVD risk in white women.

Key Words: adverse pregnancy outcomes ■ CVD risk factors ■ menopause

Pregnancy and menopause elicit profound cardiovascular changes in women.[1] Pregnancy is viewed as a stress test for future cardiovascular disease for women,[2] and adverse pregnancy outcomes, including a preterm birth (PTB) and small-for-gestational-age infant (SGA), are associated with excess cardiovascular disease (CVD) risk later in life.[3–5] At the other end of the reproductive lifespan, vasomotor symptoms of menopause, that is, hot flashes and night sweats, are also associated with higher levels of CVD risk factors.[6,7]

PTB, SGA, and vasomotor symptoms of menopause have all been independently linked to subclinical CVD, a worse CVD risk factor profile, more advanced CVD, and cardiovascular events.[7–11]

The disease process underlying PTB and/or SGA (henceforth PTB/SGA) and vasomotor symptoms of menopause may have similar or overlapping pathologies involving vascular dysfunction or impaired neurovascular control.[12–15] Given the potentially shared etiologies, women with a history of PTB/SGA may

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CLINICAL PERSPECTIVE

What Is New?

- Women with a history of a preterm birth/small-for-gestational-age infant were more likely to have severe vasomotor symptoms of menopause and had higher atherosclerotic cardiovascular disease (ASCVD) risk scores in late middle age.
- Compared with no exposures, a history of a preterm birth/small-for-gestational-age infant and vasomotor symptoms was associated with ASCVD risk score in adjusted analyses in white women.
- Women with vasomotor symptoms of menopause or a preterm birth/small-for-gestational-age infant and vasomotor symptoms of menopause were more likely to have ASCVD risk scores ≥7.5%.

What Are the Clinical Implications?

- Reproductive events throughout the life course were associated with ASCVD risk later in life, especially in white women.
- Clinicians should obtain a thorough reproductive history in patients, including details about pregnancy and menopause, to better understand ASCVD risk.

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Nonstandard Abbreviations and Acronyms

ASCVD	atherosclerotic cardiovascular disease
CARDIA	Coronary Artery Risk Development in Young Adults
CVD	cardiovascular disease
PTB	preterm birth
SGA	small-for-gestational-age infant

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be more likely to experience vasomotor symptoms of menopause later in life. Furthermore, women with a history of PTB/SGA who report vasomotor symptoms of menopause may have higher CVD risk compared with women who have experienced 1 or neither of these reproductive outcomes. Clarifying the combined effect of adverse pregnancy outcomes and menopausal symptoms on CVD risk profile could help clinicians better assess risk in women.

The purpose of the study was to determine whether women with a history of PTB/SGA were more likely to report vasomotor symptoms of menopause or severe vasomotor symptoms of menopause. We also tested the hypothesis that the estimated 10-year

atherosclerotic CVD (ASCVD) risk score[16] would be higher in women with a history of both PTB/SGA and vasomotor symptoms versus women with 1 or neither reproductive exposure.

METHODS

The CARDIA Study

The CARDIA (Coronary Artery Risk Development in Young Adults) study is a multicenter, longitudinal, population-based observational study designed to investigate the determinants of coronary heart disease and coronary heart disease risk factors in black and white women and men. At baseline (1985–1986), 5115 individuals (53% women, 52% black) aged 18 to 30 years were recruited from the following 4 metropolitan areas in the United States: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. The CARDIA study was approved by the institutional review boards at each center. All participants signed written, informed consent. The data and study materials for this investigation are available to other researchers from the CARDIA Coordinating Center (http://www.cardia.dopm.uab.edu/contact-cardia). CARDIA provides limited-access data sets from different CARDIA examinations to the National Heart, Lung and Blood Institute bioLINCC (Biologic Specimen and Data Respository Information Coordinating Center) repository (https://biolincc-nhlbi-nih-gov.pallas2.tcl.sc.edu/home/).

Of the 2787 women initially enrolled in the study, we included women who returned for the year 30 exam with evidence of menopause or perimenopause using the following criteria: self-reported menopause or hysterectomy, hot flashes or nights sweats since the age of 40 years, no menstrual cycle in the past 3 months without pregnancy, an increase in cycle length or stopped periods for any reason in the past year without pregnancy, or use of prescription or over-the-counter medications specifically to manage symptoms of menopause.[17] We excluded women with no evidence of menopausal transition (listed previously) who were younger than 51 years and women of any age who reported regular and unchanged menstrual cycles during the past year and no other indicators of menopause. Our final sample included 1866 women. Of these participants, 1800 women had complete information at year 30 for the ASCVD risk score calculation (Figure S1).

PTB and SGA

Information regarding births, gestational age at delivery, and birthweight were obtained using questionnaires in each CARDIA exam. The birthweight and sex of each baby were reported at the year 30 exam. PTB and SGA were defined as a birth that occurred at <37

completed weeks gestational age and a birthweight less than the 10th percentile for gestational age and sex, respectively.[18] A woman was classified as having PTB or SGA if either of these pregnancy outcomes was reported in any singleton birth.

Vasomotor Symptoms of Menopause

Vasomotor symptoms were assessed using a reproductive health survey in exam years 20, 25, and 30. Women were defined as having vasomotor symptoms if they replied "yes" to having hot flashes and/or night sweats in the past 3 months at exam years 20, 25, or 30. The symptoms were categorized as severe if the responses to the following questions were "a lot" or if the respondents reported visiting a doctor about their vasomotor symptoms: Did the symptoms bother you? Did the symptoms limit your activities?

Blood Pressure

Blood pressure (BP) was measured in triplicate by a trained technician at every exam in the right arm using an oscillometer (HEM907XL; Omron Corp., Schaumburg, IL) with the participant seated after a 5-minute rest. Cuff size was determined after measuring the arm at a level midway between the acromion process and olecranon. There was a 1-minute break between measurements, and the final 2 measurements were averaged for analysis. Self-report of hypertension diagnosis and treatment were noted at each exam using standardized surveys. Hypertension was defined as a BP reading of systolic BP $\geq$130, diastolic BP $\geq$80 or current use of antihypertensive medication.

Pooled Cohort Equation Risk Calculation

The pooled cohort equation ASCVD 10-year CVD risk calculator was used to estimate the 10-year risk of a hard ASCVD end point and is expressed as a percentage.[16] The prediction model includes age; race; systolic and diastolic blood pressure; total, high-density lipoprotein, and low-density lipoprotein cholesterol; smoking and diabetes mellitus history; and aspirin, statin, and antihypertensive medication use. The equation and coefficients were obtained from the CARDIA Coordinating Center.

Covariate Measurements

We included covariates measured at the most recent exam. Structured interviews or self-administered questionnaires were used to obtain the following sociodemographic information: race, age, and education level. Education level was determined as number of years of education completed. A medical history and reproductive events questionnaire were used to determine the

current use of hormone replacement therapy, parity (ie, the number of pregnancies lasting at least 20 weeks), and hysterectomy. Height was recorded to the nearest 0.5 cm and weight to the nearest 0.2 kg at each examination. Body mass index (BMI) was calculated as kg/m^2.

Statistical Analysis

We assigned women to 1 of the following 4 categories based on the presence of reproductive exposures based on the survey responses: no reproductive exposures (no PTB, SGA, or vasomotor symptoms), either PTB/SGA or vasomotor symptoms only, or both PTB/SGA and vasomotor symptoms. We tested for differences in the proportion of women with vasomotor symptoms of menopause and severe symptoms of menopause between women with and without a history of PTB/SGA using chi-square tests.

We evaluated differences in clinical and demographic characteristics and mean ASCVD risk score between different exposure groups using a Kruskal-Wallis test or 1-way ANOVA with Bonferroni post hoc tests based on the distribution of the data.

We used linear regression to determine associations of level of exposure (none, PTB/SGA only, vasomotor only, or PTB/SGA and vasomotor) with ASCVD risk score, unadjusted and then adjusted for BMI, education, study center, hysterectomy, parity, and use of hormone replacement therapy. Given the population-level race disparities in CVD burden and race-specific equations used to estimate ASCVD risk,[16,19] we tested for effect modification by performing an additional adjusted analysis with a race×exposure category interaction term included in the model. We defined high risk as an estimated 10-year ASCVD risk score of $\geq$7.5% (the cut-off for initiating statin therapy in adults aged 40–75 years)[16] and used poisson regression to evaluate the associations of exposure groups with the prevalence of high-risk scores using the same adjustment variables as the linear regression analyses.

We performed 2 sensitivity analyses by first repeating our analyses only in parous women, that is, women who reported at least 1 prebaseline or postbaseline birth to account for any long-term effect of parity itself on CVD risk,[20] and then by repeating our analyses only in women who were nulliparous at baseline. Significance was set at $P<0.05$, and Stata version 14.0 (College Station, TX) was used for analyses.

RESULTS

Participants

Of the 1866 women in the study, 324 reported no PTB/SGA or vasomotor symptoms, 118 reported

Table 1. Demographic and Clinical Characteristics of Women in CARDIA Study Exam Year 30 by Life-Course Reproductive History

	−/− (n=324)	+/− (n=118)	−/+ (n=1016)	+/+ (n=408)
Age, y*	55±1	54±1	56±1	55±1
Black race (n, %)*	120, 37	76, 64	462, 45	272, 67
Education, y*	16±1	14±1	15±1	15±1
Smoking status (n, %)*				
Current	23, 7	18, 15	121, 12	69, 17
Former	80, 25	30, 25	260, 26	97, 24
Parity (n, %)*				
0	106, 33	0, 0	370, 36	0, 0
1	68, 21	28, 24	202, 20	82, 20
≥2	150, 46	90, 76	444, 44	326, 80
BMI, kg/m2*	31.9±0.5	33.1±0.7	30.5±0.2	31.1±0.4
Hypertension (n, %)*	157, 48	67, 57	497, 49	247, 61
Diabetes mellitus (n, %)	46, 14	20, 17	133, 23	63, 15
SBP, mm Hg*	118±1	121±2	119±1	122±1
DBP, mm Hg*	72±1	74±1	73±1	75±1
TC, mg/dL	193±2	198±4	198±1	195±2
HDL-C, mg/dL*	64±1	62±2	67±1	66±1
LDL-C, mg/dL	110±2	116±3	112±1	110±2
Triglycerides, mg/dL	93±3	101±5	98±2	97±3

−/− indicates neither PTB/SGA nor vasomotor symptoms; −/+, vasomotor symptoms only; +/−, PTB/SGA only; +/+, both PTB/SGA and vasomotor symptoms. BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Parity, number of pregnancies lasting ≥20 weeks; PTB, preterm birth; SBP, systolic blood pressure; SGA, small-for-gestational-age infant; and TC, total cholesterol.

*Difference between reproductive history categories.

only PTB/SGA, 1016 reported only vasomotor symptoms, and 408 reported both PTB/SGA and vasomotor symptoms. A total of 80 women reported both PTB and SGA. The characteristics of the women in the study by reproductive exposure category are shown in Table 1. Women with both PTB/SGA and vasomotor symptoms were more likely to have been black and hypertensive, completed fewer years of education, and had higher systolic and diastolic BP compared with the women with neither reproductive exposures. Women with a history of only PTB/SGA had a higher BMI than women with no reproductive exposures.

Table 2. Atherosclerotic Cardiovascular Disease Risk Scores by Life-Course Reproductive History

	Unadjusted Mean (%)	95% CI
No exposures	3.3	2.9–3.7
PTB/SGA only	4.8*	3.6–5.9
Vasomotor only	3.8	3.5–4.0
PTB/SGA and vasomotor	4.6†	4.1–5.1

PTB indicates preterm birth; and SGA, small-for-gestational-age infant.

*A higher score than women with no exposures, P<0.05.

†Signifies a higher score vs women with no exposures or women with vasomotor exposures only.

Vasomotor Symptoms of Menopause

There was no difference in the proportion of women who experienced vasomotor symptoms between women with and without a history of PTB/SGA (78% versus 76%; P=0.43). Women with a history of PTB/SGA were more likely to have severe vasomotor symptoms of menopause (36% versus 30%; P<0.02; Table S1).

ASCVD Risk Score

ASCVD risk score ranged from 0.24% to 43% in our cohort and differed between reproductive exposure categories; women who had a history of both PTB/SGA and vasomotor exposures had higher ASCVD risk score versus women with neither exposure and a higher mean risk score than women with only the vasomotor exposure (P<0.02; Table 2). Women with PTB/SGA had higher ASCVD risk scores versus women with neither reproductive exposures (P<0.02; Table 2). In analyses stratified by race, there were no differences in ASCVD risk scores by reproductive exposure category (Table S2). The distribution of ASCVD risk scores by reproductive exposure groups is shown in Figure.

The cut-off values in Figure reflect groups for whom statins would not be recommended even with the presence of a risk enhancer, that is, a
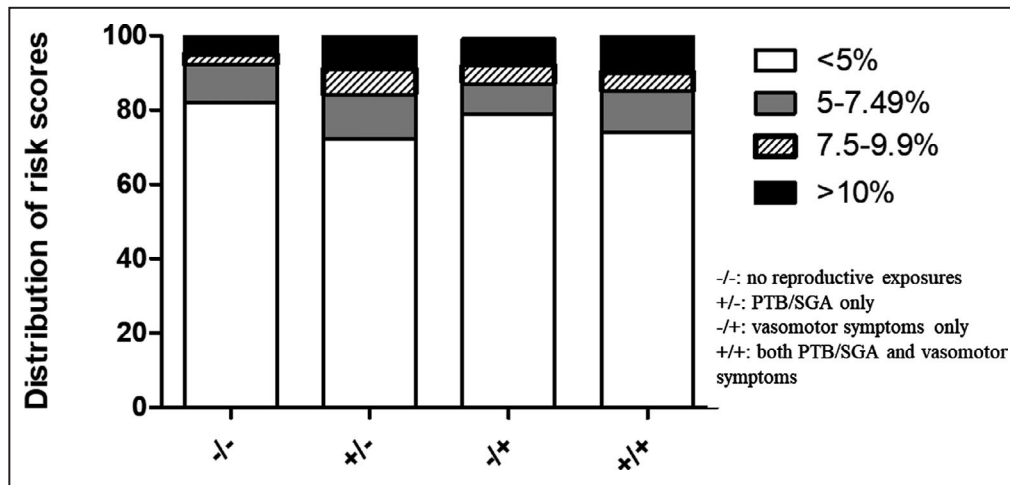
Figure. Distribution of atherosclerotic cardiovascular disease risk scores by reproductive exposure categories.
Proportion of women in each category with different levels of risk scores. <5%, initiation of statins not recommended according to 2013 guidelines even if exposed to a risk enhancer, for example, preeclampsia; <7.5%, initiation of statins not recommended for the general population according to 2013 guidelines; ≥10%, corresponds to the upper quartile of risk in the US population. –/– indicates no reproductive exposures; –/+, vasomotor symptoms exposure only; +/–, PTB/SGA only; +/+, both PTB/SGA and vasomotor symptoms. PTB indicates preterm birth; and SGA, small-for-gestational-age infant.

history of preeclampsia or other adverse pregnancy outcome (<5%), those for whom a statin would not be recommended in the absence a risk-enhancing exposure (<7.5%), and for women with higher risk, roughly equivalent to the upper quartile of risk in the general US population (≥10%).[16,21]

Regression

Reproductive exposure category was associated with ASCVD risk score. Compared with women with no reproductive exposures, a history of PTB/SGA was associated with an increase in ASCVD risk score of 1.5% (β, 1.5; 95% CI, 0.5–2.5), and a history of both PTB/SGA and vasomotor symptoms was associated with an increase in ASCVD risk score of 1.3% (β, 1.36;

95% CI, 0.6–2.0) in unadjusted analyses, whereas a history of vasomotor symptoms or both PTB/SGA and vasomotor symptoms was associated with ASCVD risk score after adjustment (Table 3).

The race×exposure category interaction was significant when added to the model, so we proceeded with stratified analyses. We found no association of reproductive exposure category with ASCVD risk score in black women, but a history of both PTB/SGA and vasomotor symptoms was associated with ASCVD risk score in white women (Table 4).

Of the 1800 women with complete data for ASCVD risk score calculation, 229 had a risk score ≥7.5%. Having a history of PTB/SGA (prevalence ratio [PR], 1.8; 95% CI, 1.0–3.2) or both PTB/SGA

Table 3. Association of Reproductive Risk Categories With Atherosclerotic Cardiovascular Disease Risk Score in Adjusted Model

	β	95% CI
No exposures	1 (reference)	
PTB/SGA only	0.82	−0.13 to 1.78
Vasomotor only	0.63	0.07 to 1.19
PTB/SGA and vasomotor	0.87	0.20 to 1.54

The linear regression model includes body mass index, education, study center, hysterectomy, parity, and current use of hormone replacement therapy. A history of vasomotor symptoms or both PTB/SGA and vasomotor symptoms was associated with atherosclerotic cardiovascular disease risk score in women. PTB indicates preterm birth; and SGA, small-for-gestational-age infant.

Table 4. Association of Reproductive Risk Categories With Atherosclerotic Cardiovascular Disease Risk Score in Black and White Women in Adjusted Model

	Black Women (n=876), β (95% CI)	White Women (n=905), β (95% CI)
No exposures	1 (reference)	1 (reference)
PTB/SGA only	0.62 (−1.10 to 2.33)	0.16 (−0.41 to 0.73)
Vasomotor only	0.65 (−0.54 to 1.85)	0.18 (−0.09 to 0.46)
PTB/SGA and vasomotor	0.31 (−1.00 to 1.62)	0.40 (0.02 to 0.78)

The linear regression model includes body mass index, education, study center, hysterectomy, parity, and current use of hormone replacement therapy. A history of both PTB/SGA and vasomotor symptoms was associated with atherosclerotic cardiovascular disease risk score in white women. PTB indicates preterm birth; and SGA, small-for-gestational-age infant.

Table 5. Association of Reproductive Risk Categories With Prevalence of Atherosclerotic Cardiovascular Disease Risk Score ≥7.5% in Adjusted Model

	PR	95% CI
No exposures	1 (reference)	
PTB/SGA only	1.40	0.82, 2.40
Vasomotor only	1.75	1.19, 2.60
PTB/SGA and vasomotor	1.60	1.04, 2.46

The poisson regression model includes body mass index, education, study center, hysterectomy, parity, and current use of hormone replacement therapy. A history of vasomotor symptoms or both PTB/SGA and vasomotor symptoms was associated with prevalence of atherosclerotic cardiovascular disease risk score ≥7.5% in women. PR indicates prevalence ratio; PTB, preterm birth; and SGA, small-for-gestational-age infant.

and vasomotor symptoms was associated with a prevalence of ASCVD risk score ≥7.5% in the unadjusted analyses (PR, 1.8; 95% CI, 1.2–2.7); a history of vasomotor symptoms and a history of both PTB/SGA and vasomotor symptoms was associated with a prevalence of ASCVD risk score ≥7.5% in the adjusted analyses (Table 5).

Sensitivity Analysis

When we limited our sample to parous women only (n=1390), all results were qualitatively similar, although the association of PTB/SGA and vasomotor symptoms with ASCVD risk score ≥7.5% only approached significance (PR, 1.5; 95% CI, 0.9–2.4; P=0.09). In our second sensitivity analysis in women who were nulliparous at baseline (n=1190; Table S3), there was no difference in mean ASCVD risk score between the categories (Table S4). A history of PTB/SGA and vasomotor symptoms trended toward a significant association with ASCVD risk score in white women (β, 0.40; 95% CI, −0.01 to 0.81). There were no significant associations of any reproductive exposure category with ASCVD risk score ≥7.5% in women who were nulliparous at baseline.

DISCUSSION

We found that the proportion of women with vasomotor symptoms of menopause was similar in women with and without a history of PTB/SGA, but the prevalence of severe vasomotor symptoms was greater among women with a history of PTB/SGA. ASCVD risk score was higher in women with both PTB/SGA and vasomotor symptoms of menopause versus women with neither exposure and higher than in women with vasomotor symptoms only, and ASCVD risk score was higher in women with PTB/SGA versus women with no reproductive exposures. A history of vasomotor symptoms or PTB/SGA and vasomotor symptoms was associated with

ASCVD risk score in our adjusted regression analyses. In analyses stratified by race, a history of PTB/SGA and vasomotor symptoms was associated with ASCVD risk scores only in white women. A history of vasomotor menopausal symptoms, with or without prior PTB/SGA, was associated with a prevalence of ASCVD risk score ≥7.5%. These data suggest that reproductive exposures are associated with ASCVD risk scores in women in late mid-life, especially in white women.

Our findings are in line with the literature documenting the associations of reproductive exposures with CVD risk factors and subclinical ASCVD. A history of PTB/SGA has been associated with a higher risk of early CVD and mortality in affected women.[11] PTB/SGA have also been linked to the development of CVD risk factors,[22] and women in the CARDIA study with a history of PTB had higher average values and steeper increases in systolic and diastolic BP and BMI 20 years later (mean age=44 years) versus women with only term births.[4] Similarly, women with vasomotor symptoms of menopause were more likely to have direct evidence of subclinical atherosclerosis, that is, coronary artery calcification, and more frequent vasomotor symptoms were linked to higher BP.[6,9]

Stratified analyses revealed that reproductive exposure categories were only associated with ASCVD risk scores in white women. The ASCVD risk calculation includes traditional CVD risk factors in separate equations for black and white women that account for a higher level of risk for black women. The fact that we only found associations of reproductive exposures with ASCVD risk scores in white women might be attributable to the fact that white women in our study had relatively low estimated risk, and perhaps reproductive exposures were more likely to influence their risk scores. We may have observed a ceiling effect in black women because of the higher level of risk accounted for by the race-specific equations. Alternatively, the excess CVD risk after PTB/SGA in black women might not be attributable to the traditional CVD risk factors included in the ASCVD risk calculations.

ASCVD risk scores are not hard outcomes, and they have important limitations. Only a small proportion of the excess CVD risk after PTB was attributable to differences in traditional risk factors in a large, population-based study,[22] so risk calculators that include only traditional risk factors might not account for PTB/SGA-specific pathways (eg, a proinflammatory and persistent anti-angiogenic state) that could mediate excess CVD risk in women with a history of PTB/SGA.[5] Along these lines, Silveira et al[8] found that hot flashes were associated with endothelial dysfunction independent of BP. Furthermore,

aortic stiffness was more likely to increase during the menopausal transition than BP or carotid intima-media thickness.[23] An earlier CARDIA investigation found no difference in carotid intima-media thickness between women with versus without a prior PTB.[4] These findings are important because CVD in women is less likely to involve obstructive coronary artery disease but more likely to be characterized by cardiovascular stiffening and endothelial dysfunction, etiologies that are shared with PTB/SGA and associated with vasomotor symptoms of menopause.[24,25] Arterial and ventricular stiffness and microvascular dysfunction are key features of diastolic dysfunction and heart failure with preserved ejection fraction, myocardial diseases that disproportionately affect women, especially black women.[19,24,26] Risk scores based on coronary and stroke outcomes that use only traditional risk factors tend to underestimate life-time risk of CVD in women and were not designed to account for heart failure risk that may be more strongly associated with reproductive exposures or black race.[27,28] Mechanisms underlying the elevated CVD risk related to reproductive events, such as heightened arterial stiffness or subclinical cardiac dysfunction, have not been well defined, especially in black women.[5]

There are notable race disparities in the rates of PTB/SGA and vasomotor symptoms of menopause in CARDIA and other studies. Others have also shown that black women are more likely to have vasomotor symptoms of menopause and PTB/SGA as well as higher rates of hypertension and more advanced CVD versus white women.[19,29–31] PTB/SGA, vasomotor symptoms of menopause, and support of BP in postmenopausal women are all influenced by vascular responses to sympathetic activity.[12,15,32] A recent study conducted only in men found that black men had greater vasoconstriction in response to bursts of muscle sympathetic nerve activity than white men, suggesting race differences in neurovascular transduction and sympathetic responsiveness.[33] Whether a neurovascular pathway contributes to race differences in rates of PTB/SGA, vasomotor symptoms of menopause, hypertension, and advanced CVD warrants further investigation.

In our sensitivity analysis, there was only a marginally significant association of ASCVD risk scores with reproductive exposure categories in white women who were nulliparous at baseline. There was no association of reproductive exposures and prevalence of ASCVD risk scores ≥7.5%, and no difference in risk scores between groups. These findings might be attributed to notable differences in biological and social risk factors between women who were parous versus nulliparous at baseline and the fact that women who were parous at baseline clustered

in certain reproductive exposure categories. The highest risk women tended to be parous at baseline, and much of the heterogeneity in demographic and clinical characteristics between reproductive exposure categories was lost when we omitted women with prebaseline births. Women who were parous at baseline were more likely to have had PTB/SGA as well as vasomotor symptoms (χ^2 $P<0.01$ for both); approximately half of the PTB/SGA group and the PTB/SGA and vasomotor symptoms group were parous at baseline. The mean ASCVD risk score was 5.7% (range, 0.26%–43%) in women who were parous at baseline versus 2.9% (range, 0.24%–30%) in women who were nulliparous at baseline. Women who were parous at baseline had higher BMI (32.8±3 kg/m^2 versus 30.0±2 kg/m^2) and fewer years of education (14±1 years versus 16±1 years) compared with women without prebaseline births, and BMI and education were associated with ASCVD risk scores in our adjusted models.

The strengths of our study include the population-based sample that included both black and white women during child-bearing and menopausal years. The sensitivity and specificity for PTB are high in the CARDIA study, but hypertensive disorders of pregnancy were not reliably captured.[4] Therefore we were not able to investigate effects of hypertensive disorders on vasomotor symptoms or ASCVD risk score in our study. We were also unable to determine whether the PTB and SGA in our study were attributed to maternal vascular dysfunction or other potential causes, such as infection, psychosocial stress, or constitutional smallness.[4,12,34] About 33% of the PTB and 30% of the SGA deliveries in the general population are related to maternal vascular dysfunction,[12] and PTB/SGA in general population-based cohorts have been associated with higher CVD risk,[11,22] so we believe our investigation was appropriate despite the unknown etiology. The CI for the association of vasomotor symptoms with or without PTB/SGA and ASCVD risk score was somewhat wide, and repeating the analysis in a larger sample might improve the understanding of the actual effect size.

In conclusion, we found that women with a prior PTB/SGA were more likely to have severe vasomotor symptoms of menopause and that a history of both PTB/SGA and vasomotor symptoms of menopause was associated with an estimated 10-year ASCVD risk in white women. Our findings suggest that the presence of both pregnancy and menopause exposures are important and that obtaining a life-course reproductive history could help clinicians assess risk in women. Future work should investigate race-specific joint associations of pregnancy and menopause exposures with hard CVD outcomes, including incident heart failure and CVD mortality.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S4
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Number and proportion of women with vasomotor symptoms of menopause by PTB/SGA history.

	No PTB/SGA *n=1340*	PTB/SGA *n=526*
No vasomotor symptoms	324, 24	118, 22
Vasomotor symptoms	1016, 76	408, 78
Severe vasomotor symptoms*	401, 30	189, 36

PTB/SGA: preterm birth and/or small-for-gestational age delivery; Women with a history of PTB/SGA were more likely to have experienced severe vasomotor symptoms of menopause versus women with no history of PTB/SGA. * indicates $p<0.02$ for comparison between groups. Data are n, %.

Table S2. Unadjusted ASCVD risk scores by life-course reproductive history in black and white women.

	ASCVD Risk in Black Women (%) n=887	ASCVD Risk in White Women (%) n=913
No exposures	5.3 (4.4, 6.2)	2.1 (1.9, 2.4)
PTB/SGA only	6.2 (4.5, 7.7)	2.3 (1.7, 3.0)
Vasomotor only	5.6 (5.1, 6.1)	2.2 (2.1, 2.4)
PTB/SGA and vasomotor	5.7 (4.9, 6.4)	2.4 (2.1, 2.8)

PTB/SGA: preterm birth and/or small-for-gestational age delivery; ASCVD: atherosclerotic cardiovascular disease. Data are mean and 95% confidence interval (CI). No differences in ASCVD risk scores by reproductive exposure category in black or white women.

Table S3. Demographic and clinical characteristics of women at Y30 who were nulliparous at baseline by life-course reproductive history.

	-/- n=247	+/- n=61	-/+ n=688	+/+ n=194
Age (yrs)*	54±1	53±1	55±1	54±1
Black Race (n, %)*	73, 30	34, 56	238, 35	98, 51
Education (yrs)*	16±1	15±1	16±1	16±1
Smoking Status (n, %)				
Current	18, 7	6, 10	62, 9	24, 13
Former	60, 25	13, 21	177, 26	42, 22
Parity (n, %)*				
0	106, 43	0, 0	370, 54	0, 0
1	53, 21	20, 33	103, 15	56, 29
≥2	85, 36	44, 67	208, 31	145, 71
BMI (kg/m^2)	30.9±0.5	31.6±1.0	29.7±0.3	29.5±0.5
Hypertension (n, %)	108, 44	28, 46	296,43	97, 50
Diabetes (n, %)	33, 13	9, 14	74, 11	22, 11
SBP (mmHg)	116±1	118±2	117±1	118±1
DBP (mmHg)	72±1	72±1	72±1	73±1
TC (mg/dL)	193±2	198±5	199±1	197±3
HDL-C (mg/dL)*	65±1	63±3	68±1	68±1
LDL-C (mg/dL)	110±2	116±5	112±1	111±2
Triglycerides (mg/dL)	92±3	95±6	94±2	91±4

PTB/SGA: preterm birth and/or small-for-gestational age delivery; **-/-**: neither PTB/SGA nor vasomotor symptoms**; +/-** PTB/SGA only; **-/+:** vasomotor symptoms only; +/+ both PTB/SGA and vasomotor symptoms; Parity: number of pregnancies lasting ≥ 20 wks; BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol. *indicates a difference between reproductive history categories.

Table S4. ASCVD risk scores by life-course reproductive history in women who were nulliparous at baseline.

	Unadjusted (%)	*95% CI*
No exposures	2.7	(2.0, 2.9)
PTB/SGA only	3.4	(2.2, 4.7)
Vasomotor only	2.9	(2.3, 2.9)
PTB/SGA and vasomotor	2.9	(2.4, 3.3)

PTB/SGA: preterm birth and/or small-for-gestational age delivery; ASCVD: atherosclerotic cardiovascular disease. Data are mean and 95% confidence interval (CI). No differences in ASCVD risk scores between categories in women who were nulliparous at baseline.

Figure S1. Study Inclusion Diagram.

2,787 women initially enrolled in CARDIA

-874 women who did not return for Y30 exam

1,913 women remaining

-47 women with no evidence of menopause or perimenopause

  -31 women <51 years of age with no evidence of menopausal transition

  -16 women of any age who reported regular and unchanged menses throughout the past year and no other evidence of menopausal transition or menopause

1,866 women included in study (476 nulliparous and 1,390 parous women)

  324 women with no reproductive exposures
  118 women with PTB/SGA only
  1016 women with vasomotor symptoms only
  408 women with PTB/SGA and vasomotor symptoms

-66 women missing information needed to calculate ASCVD risk

1,800 women included in ASCVD analysis