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Women's Reproductive History and Pre-Clinical Peripheral Arterial Disease in Late Life: The San Diego Population Study

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Abstract

Objective: Reproductive events have been linked with increased cardiovascular risk in women, but whether they are associated with pre-clinical peripheral arterial disease (PAD) has been understudied. We evaluated associations between reproductive factors and later-life ankle-brachial index (ABI), femoral artery intima-media thickness (fIMT), and femoral plaques.

Methods: Cross-sectional analysis of 707 multiethnic women who participated in a follow-up exam of the San Diego Population Study in 2007–2011. To assess associations between reproductive factors (age at menarche, parity, age at menopause, surgical menopause, hormone therapy) with ABI, and Doppler ultrasound measurements of common and superficial fIMT, linear regression was used; for femoral plaque presence, logistic regression was used. Models were adjusted for age, race/ethnicity, and cardiometabolic factors. We tested interactions of reproductive factors with menopause type (natural vs. surgical).

Results: Women were on average 71 years old, and 56% were non-Hispanic White. Reproductive factors were not associated with fIMT, femoral plaque presence, or ABI. There were significant interactions between menopause type (surgical vs. natural) and oral contraceptive use ($-\beta$: 0.04, $p = 0.03$) for ABI, as well as between menopause type and parity (β: 0.11, $p = 0.05$) and age at menopause (β: 0.001, $p = 0.05$) for fIMT. Among women with natural menopause, oral contraceptive use was associated with higher ABI (β: 0.03, $p = 0.007$) and older age at natural menopause was related to greater fIMT (β: 0.009, $p = 0.06$). Among women with surgical menopause, nulliparity was marginally associated with greater fIMT (β: 0.33, $p = 0.07$).

Conclusions: Reproductive history may not be independently associated with later-life lower extremity atherosclerosis in women. Studies are necessary to confirm findings and examine pregnancy-related exposures in relation to pre-clinical PAD.

Keywords: reproductive health, subclinical atherosclerosis, peripheral arterial disease, risk factors

Introduction

Lower extremity peripheral arterial disease (PAD) affects an estimated 8.5 million people in the United States,[1] and it is a strong predictor of total and cardiovascular mortality.[2] Recent evidence suggests that the total population burden of PAD is higher for adult women than for men age ≥40 years.[3] Major risk factors for PAD include older age, cigarette smoking, hypertension, diabetes, and dyslipidemia.[4] However, sex-specific risk factors that may underlie the presentation of PAD in women have not been well studied.

Female sex hormones, particularly estrogen, have been shown to protect women from cardiovascular disease (CVD) until menopause,[5] when the decline of ovarian hormones adversely affects CVD risk factors (*i.e.*, body fat distribution, insulin secretion, lipoproteins).[6,7] *In vitro*, estrogens have

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been shown to have metabolic actions on the liver, pancreas, and adipose tissue.[8] Studies among postmenopausal women have also shown that estrogens participate in endothelial function, including vasodilation and maintenance of vascular tone.[9] The cardioprotective effects of estrogen may explain why women develop CVD a decade later than men.[10] Similarly, it can be hypothesized that a decline in estrogen after menopause may explain the delayed, postmenopausal presentation of PAD in women.

Reproductive events in a woman's life—menarche, pregnancy, and menopause—as well as use of exogenous sex hormones may be considered markers of estrogen exposure. Earlier age at menarche has been associated with increased risk of coronary artery disease,[11] in part due to early life factors such as socioeconomic status, bodyweight, and psychosocial factors.[12,13] Pregnancy loss, which has been associated with lower estrogen concentrations,[14] has been related to increased risk of CVD in postmenopausal women.[15] In addition, risk of later-life CVD is greater among women with parity >3[16,17]; higher parity has been positively associated with inflammatory markers that are shown to be predictive of PAD.[18,19]

Earlier age at menopause and premature menopause (menopause at <40 years) have been linked to later-life cardiovascular mortality, supporting the hypothesis that longer exposure to endogenous estrogens protects against CVD.[20,21] As with earlier age at menopause, surgical menopause, amenorrhea induced after the surgical removal of ovaries, has been associated with risk of CVD, though the evidence is inconsistent.[22–24] Though hormone therapy remains the most effective treatment for menopausal vasomotor symptoms and has been shown to prevent bone loss, exogenous hormone use appears less favorable if initiated 10–20 years after menopause onset because of elevated risks of CVD and venous thromboembolism.[25] Taken together, the evidence suggests a beneficial influence of estrogen on CVD.

The few studies exploring reproductive factors and PAD found that older age at menarche[24] and hypertensive disorders during pregnancy[26] are associated with PAD (defined as ankle-brachial index [ABI] ≤0.9) in later life. However, these studies were limited by the lack of measures of pre-clinical PAD such as femoral artery intima-media thickness (fIMT) and plaque, which can detect early stages of lower extremity atherosclerosis among asymptomatic individuals.[27] Therefore, to determine whether reproductive history may serve as a marker of pre-clinical PAD in women, we examined associations between several reproductive events in a woman's life (age at menarche, parity, age at menopause, hormone therapy use) and indices of lower extremity atherosclerosis among ethnically diverse postmenopausal women in the San Diego Population Study.

The association between estrogen exposure and PAD warrants further investigation among women who experienced natural or surgically induced menopause, and consideration for the potential impact of exogenous hormone therapy use is needed. Because previous analyses have found that the association between reproductive factors and CVD differ by type of menopause (natural vs. surgical), potentially due to their impact on ovarian hormones, we further examined whether associations between reproductive history and pre-clinical PAD vary by type of menopause (natural vs. surgical).

Materials and Methods

Participants

The San Diego Population Study is a multiethnic prospective cohort study designed to examine lower extremity arterial and venous disease. Study recruitment and procedures have been published elsewhere.[28,29] Participants were current or former employees of the University of California-San Diego, or significant others of these employees, who resided in San Diego County. Between 1994 and 1998, a total of 2404 men and women aged 29–91 years were randomly selected within strata defined by age, sex, and race/ethnicity (non-Hispanic White, Hispanic, African American/Black, Asian/Pacific Islander, Native American, or Other). Women and racial/ethnic minorities (African American/Black, Hispanic, Asian) were oversampled to have adequate power to test hypotheses involving these groups.

A follow-up clinic examination was conducted between 2007 and 2011 by using the same protocol and procedures as the baseline examination. The follow-up included 1103 participants and occurred on an average of 11 years after baseline. For the current analysis, we limited our sample to women who had completed a reproductive history assessment, and who had attended a follow-up clinical examination during which femoral artery atherosclerosis was measured ($n = 735$). Women who reported that they were ''uncertain'' about type of menopause ($n = 24$) and women with ABI ≥1.4 ($n = 4$) were excluded. On exclusions, our final sample size was 707 women. All participants provided written informed consent. The study received approval from the Institutional Review Board at the University of California-San Diego.

Reproductive history exposures

Reproductive history in the San Diego Population Study was assessed *via* an interviewer-administered questionnaire. Information was collected regarding age at menarche, gravidity (number of pregnancies), parity (number of live births), menopausal status, age at menopause, oral contraceptive and menopause hormone therapy use, and duration (in years) of hormone therapy use. However, we categorized a woman as having any pregnancy loss if gravidity minus parity was ≥1. Women were asked whether menopause was reached naturally or induced surgically, and they were, in addition, asked whether they had a hysterectomy (''with removal of both ovaries,'' ''without removal of both ovaries,'' ''uncertain''). Reproductive duration was defined as age at menopause minus age at menarche. Previous studies demonstrated that the validity of self-reported menopausal status (and type) ranges from 71% to 95%, and that the validity of age at menopause is 64%–80%.[30,31] Reproductive history was retrieved from the baseline study visit. For 149 women who were not postmenopausal at baseline, menopause history (*i.e.*, age at menopause, type of menopause) was retrieved from the follow-up examination.

Subclinical measures of PAD

Ankle-brachial index. ABI was measured at the follow-up clinical exam, with the participant in a supine position. Systolic blood pressure was measured twice from both brachial arteries and from both the dorsalis pedis and posterior tibial arteries. The ABI for each side was calculated as the

maximum of the average systolic blood pressure of the dorsalis pedis or posterior tibial divided by the average of the two higher brachial arterial systolic pressures. The overall ABI was defined as the lower of the left and right ABI.

Femoral IMT and plaque. Images of the left and right superficial and common femoral arteries were obtained by using Doppler ultrasound (Acuson Aspen; Siemens, Inc.), as previously described.[27] Trained ultrasound technicians used Carotid Analyzer software from the Vascular Research Tools 5 Suite (Medical Imaging Applications, LLC, Coralville, IA) to measure the IMT and to determine the presence and extent of plaque. The common and superficial femoral IMTs (sfIMTs) were calculated (regardless of plaque presence) as the average of the far wall of both the left and right femoral arteries. Both inter- and intra-reader intra-class correlations were >80% for common femoral IMT (cfIMT) and >75% for sfIMT.[27]

Plaque presence was defined by the Mannheim and American Society of Echocardiography consensus statements as a distinct area protruding into the arterial lumen that was at least 50% thicker than the adjacent IMT, or thickness >1.5 mm from the media adventitia border to the intima-lumen border.[32,33] Plaque presence included presence in any of the four measured segments, the left and right superficial and common femoral. Plaques identified in each of the femoral artery segments were classified as ''definite'' or ''probable'' due to the presence of artifact in some images. Sensitivity analyses were conducted excluding the ''probable'' plaques ($n=4$, 2.8%).

Covariates

Demographic and socioeconomic characteristics, including age, race/ethnicity, and education, were assessed by self-report using an interviewer-administered questionnaire. Smoking was defined as ever having smoked versus never. Physical activity was determined by asking the following question: ''Compared to other persons your age, how would you describe your level of physical activity?'' Weight (in kilograms) and height (in centimeters) were measured, and the body mass index (BMI) was calculated as kg/m^2. Systolic and diastolic blood pressures were assessed in the right arm for each participant after 5 minutes of rest.

Non-fasting blood samples were drawn. Samples were stored at −80°C and sent to a laboratory where they were analyzed within 24 hours. Direct enzymatic assays were used to determine total and high-density lipoprotein cholesterol on the Roche Cobas 6000 analyzer (Roche Diagnostics Corporation, Indianapolis, IN).[26] Low-density lipoprotein cholesterol was calculated by using the Friedewald equation.[34]

A medication inventory was conducted to obtain information on a lipid-lowering treatment, diabetes mediations, and anti-hypertensive medication use. Dyslipidemia was defined as a ratio of total cholesterol to high-density lipoprotein cholesterol >5.0,[35] or use of lipid-lowering medications at baseline. Diabetes mellitus was defined as self-reported diabetes mellitus, or use of oral hypoglycemic medications and/or insulin. Hypertension was defined as a systolic pressure ≥140 mmHg and/or a diastolic pressure ≥90 mm Hg, and/or use of anti-hypertensive medications. Prevalent PAD was defined as ABI <0.9. Prevalent CVD included a history of previous myocardial infarction, stroke, angioplasty, or revascularization, and it was assessed *via* self-report.

Statistical analysis

Analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, NC). Data were examined for distribution and outliers. Continuous variables were assessed for normality with the Shapiro-Wilk normality test. Participant characteristics and measures of lower extremity atherosclerosis were compared by type of menopause (natural vs. surgical) using Student's *t*-test or the Mann–Whitney U test for continuous variables, and χ^2 or Fisher's exact tests for categorical variables. The ABI as well as common and superficial fIMT were modeled by using linear regression. Plaque presence (yes/no) was modeled by using logistic regression. Unadjusted analyses were performed to examine associations between reproductive exposures and our outcomes. Reproductive factors associated with measures of lower extremity atherosclerosis at $p \leq 0.20$ were entered in multiple linear and logistic regression models adjusting for age, race/ethnicity, and covariates traditionally associated with PAD or our outcomes of interest at $p < 0.1$ (*i.e.*, BMI, smoking status, physical activity, systolic blood pressure, lipids, diabetes). We tested for interactions between reproductive factors and surgical menopause by using additive interactions in the linear regression models and multiplicative interactions in the logistic regression models. Stratified analyses were performed for interactions with $p < 0.10$ by separately modeling associations according to the potential moderating factor (*e.g.*, natural vs. surgical menopause). Sensitivity analyses were performed while excluding probable plaques. Additional sensitivity analyses were performed while excluding women who reported ever using oral contraceptives or menopause hormone therapy, when appropriate ($n=475$). Residual analyses were conducted to verify model assumptions and examine for multicollinearity. If a variable had a variance inflation factor ≥5, we examined its correlation with other variables and removed covariates that were highly correlated (≥0.7) to other variables. Because these analyses were hypothesis-deriving, we did not account for multiple testing. *Post hoc* power calculations were performed estimates from prior studies.[24,27] Using a 5% alpha level, we had 90% to estimate differences in ABI and 41% power for fIMT measures and plaque.

Results

Participant characteristics are presented in Table 1. Mean age at time of femoral artery measures was 70.6 years (standard deviation = 9.6). The majority of our sample (56%) self-identified as non-Hispanic White. The mean ages at menarche and menopause were 12.6 and 48.2 years, respectively. Nearly 30% ($n=201$) of women reported a history of surgical menopause. Compared with women with natural menopause, women with surgical menopause were older, more likely to self-identify as African American, had a significantly shorter reproductive duration, and were more likely to report having ever used menopause hormone therapy. The surgical menopause group had higher systolic blood pressure (136.1 ± 21.0 vs. 129.5 ± 17.5; $p=0.0001$) and lower ABI values (1.08 ± 0.12 vs. 1.11 ± 0.11; $p=0.007$).

Table 1. Participant Characteristics ($N=707$)

	Total sample (n = *707*)	*Natural menopause* (n = *506*)	*Surgical menopause* (n = *201*)	p
Age	70.6 ± 9.6	69.6 ± 9.7	72.90 ± 9.0	<0.0001
Race/ethnicity				0.0001
Non-Hispanic White	397 (56.2)	297 (58.7)	100 (49.8)	
African American	94 (13.3)	49 (9.7)	45 (22.4)	
Hispanic/Latino	119 (16.8)	86 (17.0)	33 (16.4)	
Asian/Pacific Islander/Native American/Other	97 (13.7)	74 (14.6)	23 (11.4)	
Education ($n=701$)				0.0008
≤High school	67 (9.6)	39 (7.8)	28 (14.0)	
Some college	281 (40.1)	189 (37.7)	92 (46.0)	
College degree/post college	353 (50.4)	273 (54.5)	80 (40.0)	
Reproductive history				
Age at menarche	12.6 ± 1.5	12.6 ± 1.6	12.8 ± 1.5	0.12
Early menarche (<12 years)	138 (19.5)	102 (20.2)	36 (17.9)	0.50
Gravidity ($n=602$)	3.2 ± 1.9	3.2 ± 1.8	3.3 ± 2.0	0.24
Pregnancy loss ($n=593$)	247 (41.7)	174 (41.7)	73 (41.5)	0.96
Parity ($n=603$)				0.87
0	37 (6.1)	28 (6.6)	9 (5.0)	
1	91 (15.1)	63 (14.9)	28 (15.6)	
2	217 (36.0)	154 (36.3)	63 (35.2)	
≥3	258 (42.8)	179 (42.2)	79 (44.1)	
Age at menopause ($n=692$)	48.2 ± 6.3	50.3 ± 4.2	42.8 ± 7.4	<0.0001
Reproductive duration ($n=692$)	35.5 ± 6.5	37.8 ± 4.4	30.0 ± 7.5	<0.0001
Oral contraceptive use ever ($n=701$)	427 (60.9)	310 (62.0)	117 (58.2)	0.35
Duration of oral contraceptive use (years)	1 (0–5)	1 (0–5)	1 (0–5)	0.22
Menopause HT use ever ($n=698$)	475 (68.1)	305 (61.2)	170 (85.0)	<0.0001
Duration of menopause HT use (years)	5 (0–15)	2 (0–10)	15 (4–25)	<0.0001
PAD risk factors and subclinical measures				
BMI, kg/m^2	27.0 ± 5.6	26.9 ± 5.6	27.3 ± 5.6	0.42
Ever smoker ($n=702$)	215 (30.6)	150 (29.9)	65 (32.5)	0.50
Physical activity ($n=703$)				0.54
Less active	108 (15.4)	75 (14.9)	33 (16.5)	
Same active	189 (26.9)	141 (28.0)	48 (24.0)	
More active	406 (57.8)	287 (57.1)	119 (59.5)	
Systolic blood pressure, mmHg	131.4 ± 18.8	129.5 ± 17.5	136.1 ± 21.0	0.0001
Diastolic blood pressure, mmHg	74.4 ± 10.1	74.1 ± 10.1	75.0 ± 10.2	0.27
Total cholesterol, mg/dL ($n=677$)	204.6 ± 38.7	203.2 ± 38.2	208.2 ± 39.8	0.13
LDL cholesterol, mg/dL ($n=697$)	112.7 ± 34.6	112.0 ± 35.0	114.4 ± 33.5	0.41
HDL cholesterol, mg/dL ($n=697$)	65.1 ± 20.3	64.7 ± 20.9	66.2 ± 18.9	0.37
Prevalent hypertension	447 (63.2)	303 (59.9)	144 (71.6)	0.003
Prevalent diabetes	69 (9.8)	46 (9.1)	23 (11.4)	0.34
Prevalent PAD (ABI <0.9)	23 (3.3)	14 (2.8)	9 (4.6)	0.36
Prevalent CVD	45 (6.4)	25 (4.9)	20 (10.0)	0.02
ABI ($n=696$)	1.1 ± 0.11	1.11 ± 0.10	1.08 ± 0.12	0.007
cfIMT, mm ($n=651$)	0.84 ± 0.42	0.83 ± 0.40	0.86 ± 0.45	0.48
sfIMT, mm	0.58 ± 0.11	0.57 ± 0.11	0.58 ± 0.09	0.21
Plaque presence ($n=731$)	140 (19.8)	98 (19.4)	42 (20.9)	0.64

ABI, ankle-brachial index; BMI, body mass index; CVD, cardiovascular disease; cfIMT, common femoral intima-media thickness; GSM, gray scale median; HDL, high-density lipoprotein; HT, hormone therapy; IMT, intima-media thickness; LDL, low-density lipoprotein; PAD, peripheral artery disease; sfIMT, superficial femoral intima-media thickness.

Table 2 presents associations between reproductive factors and sfIMT, cfIMT, femoral plaques, and ABI in our total sample. Unadjusted analyses found that surgical menopause, ever use of menopause hormone therapy, and duration of menopause hormone therapy were inversely associated with ABI. Older age at menopause and ever having used oral contraceptives were associated with higher ABI, but associations were attenuated once adjusting for age at the follow-up clinical exam. Reproductive history was not significantly associated with ABI in fully adjusted models, which accounted for age, race/ethnicity, BMI, smoking, physical activity, blood pressure, lipids, and diabetes status.

In unadjusted models, ever use of oral contraceptives and duration of use were associated with lower cfIMT and sfIMT

Table 2. Associations Between Reproductive Factors and Subclinical Measures of Peripheral Arterial Disease in the Total Sample ($N = 707$)

	Unadjusted, β *(SE)*	*Fully adjusted,* β *(SE)*	*Unadjusted,* β *(SE)*	*Fully adjusted,* β *(SE)*	*Unadjusted,* β *(SE)*	*Fully adjusted,* β *(SE)*
Separate predictors	*ABI*		*cfIMT*		*sfIMT*	
Age at menarche	0.001 (0.003)		–0.004 (0.01)		–0.002 (0.003)	
Early menarche (<12 years)	–0.01 (0.01)		0.019 (0.04)		–0.0009 (0.01)	
Gravidity ($n = 618$)	–0.005 (0.002)	–0.0004 (0.002)	–0.006 (0.01)		0.0003 (0.002)	
Pregnancy loss ($n = 593$)	–0.002 (0.009)		–0.001 (0.037)		–0.001 (0.009)	
Parity ($n = 618$)						
0	–0.004 (0.019)	–0.008 (0.018)	0.0001 (0.08)	0.035 (0.077)	–0.003 (0.019)	
1	0.024 (0.013)	0.024 (0.013)	–0.06 (0.05)	–0.048 (0.052)	0.007 (0.013)	
2 (Reference)	—	—	—	—	—	
≥3	–0.014 (0.01)	–0.001 (0.009)	0.02 (0.04)	–0.031 (0.039)	0.007 (0.009)	
Surgical menopause	–0.028 (0.01)[a]	–0.009 (0.009)	0.03 (0.04)		0.011 (0.009)	
Age at menopause	0.001 (0.001)[b]	0.001 (0.001)	0.002 (0.003)		–0.0008 (0.0007)	
Reproductive duration (per year)	0.001 (0.001)	0.004 (0.001)	0.002 (0.003)		–0.0007 (0.0006)	
Oral contraceptive use ever	0.04 (0.01)[c]	0.02 (0.01)	–0.10 (0.03)[a]	–0.004 (0.036)	–0.025 (0.008)[a]	–0.005 (0.009)
Duration of oral contraceptive use (years)	0.001 (0.001)	–0.0001 (0.0007)	–0.007 (0.003)[a]	–0.003 (0.003)	–0.002 (0.0007)[a]	–0.0008 (0.0007)
Menopause HT use ever	–0.03 (0.01)[d]	–0.005 (0.009)	0.001 (0.03)		0.007 (0.008)	
Duration of menopause HT use (years)	–0.002 (0.0004)[c]	–0.0003 (0.0004)	0.003 (0.002)[b]	–0.002 (0.002)	0.0003 (0.0004)	

Fully adjusted model: age, race/ethnicity, BMI, systolic blood pressure, total cholesterol, high-density lipoprotein, ever smoker, physical activity, and diabetes. Models were examined for effect modification by race/ethnicity and were stratified if an interaction was observed at $p \leq 0.1$. Only variables with $p \leq 0.20$ in univariate analyses were tested in fully adjusted models.
[a]$p < 0.01$; [b]$p < 0.05$; [c]$p < 0.0001$; [d]$p < 0.001$.
SE, standard error.

Table 3. Associations Between Reproductive Factors and Femoral Plaque Presence

Separate predictors	*Unadjusted, OR (95% CI)*	p	*Fully adjusted, OR (95% CI)*	p
Age at menarche	1.01 (0.90–1.14)	0.84		
Early menarche (<12 years)	1.01 (0.63–1.61)	0.96		
Gravidity	1.07 (0.95–1.20)	0.26		
Parity ($n=121$)				
0	1.00 (0.43–2.32)	0.99		
1	1.19 (0.64–2.19)	0.59		
2 (Reference)	—	—		
≥3	1.10 (0.71–1.72)	0.67		
Hysterectomy (any)	0.98 (0.66–1.43)	0.90		
Surgical postmenopause	0.89 (0.59–1.33)	0.56		
Age at menopause	1.00 (0.97–1.03)	0.84		
Reproductive duration	1.00 (0.97–1.03)	0.89		
Oral contraceptive use ever	2.14 (1.48–3.10)	<0.0001	1.31 (0.84–2.05)	0.24
Duration of oral contraceptive use (years)	1.05 (1.01–1.10)	0.01	1.02 (0.98–1.06)	0.30
Menopause HT use ever	1.00 (0.68–1.47)	0.99		
Duration of menopause HT use (years)	0.98 (0.97–0.99)	0.03	1.01 (0.99–1.03)	0.23

Fully adjusted model: age, race/ethnicity, BMI, systolic blood pressure, total cholesterol, high-density lipoprotein, ever smoker, physical activity, and diabetes. Models were examined for effect modification by race/ethnicity and stratified if an interaction was observed at $p \leq 0.1$. Only variables with $p \leq 0.20$ in univariate analyses were tested in fully adjusted models.

CI, confidence interval; OR, odds ratio.

(Table 2). Unadjusted analyses also found that duration of menopause hormone therapy was associated with a 0.003-mm ($p=0.03$) greater cfIMT (standardized β: 0.09). However, associations between oral contraceptives and IMT measures were attenuated in fully adjusted models. After adjusting for covariates, we found significant interactions between surgical menopause and oral contraceptive use ($-\beta$: 0.04, $p=0.03$) for ABI, and between parity (β: 0.11, $p=0.05$) and age at menopause (β: 0.001, $p=0.05$) for cfIMT. Stratified analyses by type of menopause are described later.

Associations between reproductive factors and femoral plaque are shown in Table 3. Oral contraceptive use was associated with significantly greater odds of femoral plaque in unadjusted analyses (odds ratio [OR]: 2.14, 95% confidence interval [CI]: 1.48–3.10). Longer duration of menopause hormone therapy was associated with marginally lower odds of femoral plaque (OR: 0.98, 95% CI: 0.97– 0.99) in unadjusted analyses. Associations were attenuated (OR: 1.01, 95% CI: 0.99–1.03) in fully adjusted models, and there were no significant interactions with surgical menopause. Sensitivity analyses excluding probable plaque did not impact our findings.

Given the significant interaction between surgical menopause and oral contraceptive use for ABI, we stratified analyses by type of menopause (Fig. 1a, b). Among women with a history of natural menopause, ever use of oral contraceptives was associated with higher ABI (β: 0.03, $p=0.007$). Among women who reported surgical menopause, there was no significant association between oral contraceptive use and ABI. In addition, there were no significant associations between menopause hormone therapy use and ABI in stratified analyses.

Stratified analyses for cfIMT are presented in Table 4. Among women with natural menopause, older age at menopause was associated with 0.01-mm ($p=0.03$) greater cfIMT (standardized β: 0.10); the association was marginally significant in fully adjusted models (β: 0.009, $p=0.06$; standardized β: 0.09) and was attenuated in sensitivity analyses excluding hormone users. Oral contraceptive use was associated with 0.08-mm ($p=0.04$) lower cfIMT in unadjusted analyses among women with natural menopause (standardized β: –0.09) and 0.15-mm ($p=0.03$) lower cfIMT among women with surgical menopause (standardized β: –0.17). Among women with surgical menopause, nulliparity (vs. two births) was marginally associated with 0.33-mm ($p=0.07$) greater cfIMT (standardized β: 0.14).

Discussion

This study found that among a multiethnic cohort of healthy older women, reproductive history did not significantly influence lower extremity atherosclerosis measures, though the association between reproductive factors and subclinical atherosclerosis varied by type of menopause (natural vs. surgical). Reproductive events across a woman's life, including menarche, pregnancy, and menopause, have been associated with later-life CVD potentially through pathways involving hormonal and metabolic alterations.[36,37] However, our results are consistent with a cross-sectional analysis by Stockl et al.,[24] which found that parity, age at menopause, reproductive duration, use of hormone therapy, and surgical menopause were not significantly associated with lower extremity subclinical atherosclerosis. It is possible that unlike CVD, reproductive aging is not associated with lower extremity atherosclerosis independently from chronological aging. To further investigate this claim, future studies are necessary for evaluating changes in measures of pre-clinical PAD during the menopause transition, or for directly examining associations between endogenous sex hormones and indicators of pre-clinical PAD in women. It is also possible that we were unable to detect an association between reproductive factors and lower extremity atherosclerosis because of the low risk of PAD or CVD in this healthy population. Since atherosclerosis develops slower in the superficial femoral artery compared with the coronary and carotid arteries,[38] it is possible that associations between

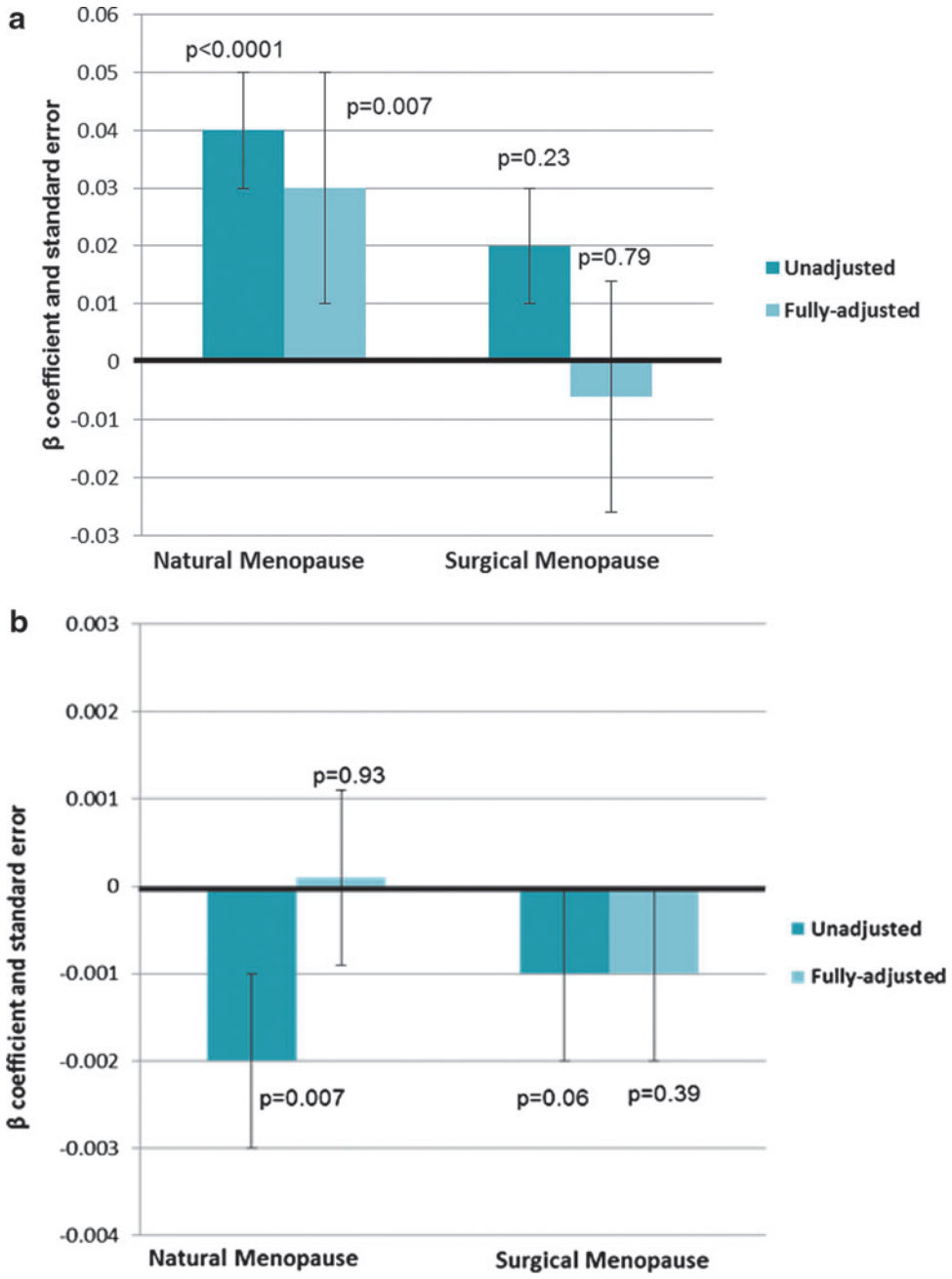

FIG. 1. **(a)** Association between ever use of contraceptives (yes vs. no) and ankle-brachial index by type of menopause (natural/surgical). Fully adjusted model = age, race/ethnicity, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein, ever smoker, physical activity, and diabetes. **(b)** Association between ever use of menopause hormone therapy (yes vs. no) and ankle-brachial index by type of menopause (natural/surgical). Fully adjusted model = age, race/ethnicity, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein, ever smoker, physical activity, and diabetes.

reproductive factors and lower extremity atherosclerosis may not be detectable until there is a severe degree of stenosis.

Although surgical menopause was not significantly associated with our measures of lower extremity atherosclerosis, women with surgical menopause had a more adverse CVD risk profile, and the observed associations varied by type of menopause (natural vs. surgical). The surgical removal of the ovaries is associated with a sudden cessation of ovarian estrogen production in contrast to the declines in estrogen levels occurring over time during the menopausal transition.[39] It has been hypothesized that this dramatic decline in estrogen is associated with greater cardiometabolic risk,[40,41] and it increases risk of thrombotic events.[42] However, our results are consistent with recent studies that have shown that surgical menopause is not independently associated with venous thromboembolism or CVD mortality.[24,43] Current evidence suggests that CVD risk among women with surgical menopause is limited to women age <50 years at the time of surgical menopause[23] or without estrogen treatment.[22] We were unable to further explore this claim given that the number of women with early or premature menopause was too low to yield meaningful estimates when stratifying by type of menopause. However, our analyses found significant interactions between other reproductive factors (*i.e.*, hormone therapy use, parity) and surgical menopause in relation to ABI and cfIMT. These findings are in agreement with a previous analysis of the Women's Health Initiative, which found that associations between reproductive history and incident heart failure hospitalization vary by type of menopause; with heart failure, longer reproductive duration was

Table 4. Associations Between Reproductive Factors and Common Femoral Intima-Media Thickness by Type of Menopause

Separate predictors	*Unadjusted, β (SE)*	p	*Fully adjusted, β (SE)*	p
Natural menopause				
Parity ($n=391$)				
0	−0.12 (0.09)	0.20	−0.04 (0.10)	0.71
1	−0.05 (0.06)	0.45	−0.03 (0.07)	0.66
2 (Reference)	—	—	—	—
≥3	0.05 (0.05)	0.32	0.01 (0.05)	0.78
Age at menopause ($n=454$)	0.01 (0.005)	0.03	0.009 (0.005)	0.06
Reproductive duration (per year)	0.009 (0.004)	0.06	0.001 (0.0006)	0.11
Oral contraceptive use ever ($n=462$)	−0.08 (0.04)	0.04	0.02 (0.04)	0.73
Duration of oral contraceptive use (years)	−0.006 (0.003)	0.08	−0.001 (0.003)	0.77
Surgical menopause				
Parity ($n=162$)				
0	0.32 (0.18)	0.08	0.33 (0.18)	0.07
1	−0.12 (0.11)	0.30	−0.16 (0.11)	0.16
2 (Reference)	—	—	—	—
≥3	−0.09 (0.08)	0.26	−0.08 (0.08)	0.30
Age at menopause ($n=181$)	0.0003 (0.005)	0.94	−0.0008 (0.005)	0.87
Reproductive duration (per year)	0.0007 (0.005)	0.88	−0.0007 (0.005)	0.89
Oral contraceptive use ever ($n=182$)	−0.15 (0.07)	0.03	−0.08 (0.08)	0.32
Duration of oral contraceptive use (years)	−0.01 (0.006)	0.05	−0.007 (0.007)	0.30

Fully adjusted model: age, race/ethnicity, BMI, systolic blood pressure, total cholesterol, high-density lipoprotein, ever smoker, physical activity, and diabetes. Models were examined for effect modification by race/ethnicity and stratified if an interaction was observed at $p \leq 0.1$. Only variables with $p \leq 0.20$ in univariate analyses were tested in fully adjusted models.

associated with hospitalization among women with natural menopause and not surgical menopause.[36]

Among women with natural menopause, oral contraceptive use was significantly associated with higher ABI. Our findings are consistent with a prior investigation that found less coronary artery disease among women with past oral contraceptive use.[44] Oral contraceptives are one of the most common risk factors for peripheral vascular disease among younger women,[45,46] potentially due to their positive association with coagulation factors.[47,48] However, the evidence relating oral contraceptive use to atherosclerotic disease in postmenopausal women has been mixed.[44,49] Yet, these previous analyses did not examine whether the association between oral contraceptive use and PAD differs by type of menopause (natural vs. surgical). It is possible that the protective effect of oral contraceptives among older women with natural menopause is due to the delay of menopause with oral contraceptive use.[50] Whether our results differ by dose or type of oral contraceptive could not be determined.

Age at menopause was not independently associated with our measures of lower extremity atherosclerosis, but there was a marginal statistical association between older age at natural menopause and cfIMT. This finding is surprising given that older age at natural menopause has been associated with lower risk of CVD, potentially due to longer exposure to endogenous sex hormones.[36,51] However, a prior study found no significant association between age at menopause and PAD,[24] whereas a more recent analysis found a U-shaped association whereby early onset (age <40 years) and late onset (age >55 years) of menopause were related to non-procedure-related vascular thrombotic events.[43] Therefore, further analyses are necessary to clarify the association between age at menopause and pre-clinical PAD among women with and without surgical menopause. It is also possible that the association between age at menopause and lower extremity subclinical atherosclerosis is not causal and may, in part, be due to prior CVD risk factors, which have been associated with younger age at natural menopause (*e.g.*, history of smoking, greater BMI, lower socioeconomic status).[52]

Although previous analyses have found that women with <2 births and those with ≥3 births are at increased risk for CVD,[17] these findings have not been consistent.[53,54] Among participants in the KORA F4 study, there was no significant relationship between parity and PAD.[24] In the present analysis, we found that among women with surgical menopause, compared with two births, nulliparity was associated with greater cfIMT. Though the association was marginally significant, the direction of the association is consistent with recent studies that found that nulliparity is associated with incident heart failure and worse markers of subclinical CVD.[36,55] Our findings may be due to earlier life cardiometabolic factors that were not assessed in this study. In addition, we did not collect information on reasons for nulliparity or surgical menopause, which may include endocrine disorders (*e.g.*, polycystic ovarian syndrome), endometriosis, cancer prevention or management, and personal choice, all of which (with the exception of personal choice) have been associated with higher risk for CVD.[56]

Our study has several strengths and limitations that should be noted. We used a large multiethnic population-based cohort, the San Diego Population Study, that was specifically designed to examine lower extremity venous disease and arterial disease by using standardized clinic examinations. However, our analysis was cross-sectional in design, and, thus, causation cannot be determined. Also, reproductive history was determined based on self-report and we did not have data on the underlying reasons for surgical menopause, which may impact likelihood of exposure to oral contraceptives

and duration of use. However, previous analyses have determined that reliability of several self-reported reproductive characteristics is good (*e.g.*, age at menarche, parity, age at menopause, type of menopause).[30,31] Selection bias may be present given that the participants were current or former employees of the University of California-San Diego, limiting the generalizability of our findings. Notably, several important reproductive characteristics were not available in our data, including type of pregnancy loss, age at first birth, adverse pregnancy outcomes (preterm birth, hypertensive disorders of pregnancy, gestational diabetes), and other reproductive disorders. The use of subclinical markers of lower extremity atherosclerotic disease was a strength in this analysis; these measures allow us to reliably detect early-stage disease in this older healthy population.[57] Though it is possible that earlier life risk factors may play a role in development of PAD, these data were not available.

Conclusions

This is the first study to our knowledge to examine the impact of several reproductive characteristics on indicators of pre-clinical PAD. Our findings suggest that reproductive events in a woman's life may not significantly influence measures of lower extremity atherosclerosis. However, associations between reproductive characteristics and preclinical PAD may differ by type of menopause (natural vs. surgical), with oral contraceptive use being associated with higher ABI among women with natural menopause and older age at natural menopause being associated with greater cfIMT. We also found that nulliparity may be an additional risk factor for pre-clinical PAD among women with surgical menopause. Collectively, our analyses suggest that reproductive history may not play a major role in risk of lower extremity atherosclerosis among women. However, larger prospective studies are necessary to confirm our findings and to examine the impact of additional reproductive characteristics, particularly pregnancy-related outcomes, on lower extremity atherosclerosis.

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Authors' Contributions

Authors contributed to the works as follows: study conception and design (Y.I.C., N.P., C.L.W.), acquisition of data (M.A.A., M.H.C., E.B.-M., N.S.), statistical analysis (Y.I.C.), interpretation of data (all authors), and drafting of article (all authors). All authors gave final approval of the version submitted for publication.

Author Disclosure Statement

No competing financial interests exist.

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