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Pregnancy-related events associated with subclinical cardiovascular disease burden in late midlife: SWAN

Yamnia I. Cortés^{a,*}, Janet M. Catov^{b,c}, Maria Brooks^d, Samar R. El Khoudary^d, Rebecca C. Thurston^{d,e}, Karen A. Matthews^{d,e}, Carmen R. Isasi^f, Elizabeth A. Jackson^g, Emma Barinas-Mitchell^d

^aSchool of Nursing, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

^bDepartments of Obstetrics, Gynecology, and Reproductive Sciences and Epidemiology, University of Pittsburgh School of Medicine and Graduate School of Public Health, Pittsburgh, PA, USA

^cDepartment of Magee-Women's Research Institute, Pittsburgh, PA, USA

^dDepartment of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA

^eDepartment of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

^fDepartment of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA

^gSchool of Medicine, The University of Alabama at Birmingham, Birmingham, AL, USA

Abstract

Background and aims: Reproductive factors are associated with later life CVD in women (e.g., age at first birth, preeclampsia, gestational diabetes), but studies have focused largely on premenopausal women. We examined the relationship of reproductive factors with subclinical CVD burden in late midlife women.

Methods: We included 964 parous women from the Study of Women's Health Across the Nation (SWAN), who completed a reproductive history questionnaire at the 13th SWAN visit (2011–2012), and a carotid ultrasound and brachial-ankle pulse wave velocity (baPWV) assessment. The primary outcomes were carotid intima-media thickness, plaque, and baPWV; our secondary outcome was a composite subclinical CVD index created using these measures. Linear and logistic regression was performed to examine associations with individual subclinical CVD measures, and

*Corresponding author. School of Nursing, The University of North Carolina at Chapel Hill Campus Box 7460 Chapel Hill, NC, 27599-7460, USA. yicortes@email.unc.edu (Y.I. Cortés).

Author contributions

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Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2019.07.012>.

multinomial logistic regression was used in analyses of the composite index. Models adjusted for socio-demographics and cardiovascular risk factors.

Results: Mean age at subclinical CVD assessment was 60.2 years ($SD \pm 2.7$). History of gestational hypertension/preeclampsia was associated with greater carotid IMT (β : 0.038, $p = 0.004$). Earlier age at first birth was associated with subclinical CVD, but not when accounting for CVD risk factors. History of gestational diabetes was associated with greater baPWV, but not related to our composite index.

Conclusions: Pregnancy history is an important marker of subclinical CVD in late midlife and may impact the vasculature through distinct pathways. Future studies are necessary to evaluate racial/ethnic differences in the observed associations and to assess the benefit of a composite subclinical CVD index for earlier CVD risk modification in midlife women.

Keywords

Cardiovascular disease; Midlife; Reproductive history; Subclinical atherosclerosis; Women's health

1. Introduction

Despite improvement in cardiovascular disease (CVD) morbidity and mortality, CVD remains the leading cause of death among women in the United States [1]. It has been suggested that identifying sex-specific risk factors for CVD may improve screening, diagnosis, and management of CVD among women [2]. Important reproductive factors associated with later life CVD include earlier age at menarche [3], parity [4], lack of breastfeeding [5], hypertensive disorders of pregnancy [6], gestational diabetes [7], and preterm birth [8]. The mechanisms through which earlier age at menarche has been linked to CVD risk in later life include greater adiposity and insulin resistance [9,10]. Similarly, higher parity and younger age at first birth have been associated with greater body mass index (BMI) in adulthood [11]. Breastfeeding has been shown to release oxytocin, which reduces cardiovascular and sympathetic reactivity to stress [12]. Preeclampsia is associated with an increased mean arterial pressure, hyperlipidemia, and insulin resistance during pregnancy and postpartum [13], whereas a more extreme insulin resistance and adiposity is associated with gestational diabetes [14]. In a previous analysis, we found that a history of preterm birth is associated with higher blood pressure in late midlife [15]. However, there is limited evidence regarding the effect of reproductive factors on subclinical markers of CVD in midlife, a period associated with greater progression of subclinical CVD [16].

Subclinical CVD, a strong predictor of incident cardiovascular events, can be measured using various methods across a number of vascular beds (e.g., carotid intima-media thickness [IMT] and plaque, brachial-ankle pulse wave velocity [baPWV], coronary artery calcification) [17-19]. In recent years, adverse pregnancy outcomes (e.g., preterm birth, preeclampsia, gestational diabetes) have been related to greater carotid IMT [14,20,21], a non-invasive validated and reliable marker of subclinical vascular remodeling and damage [18] assessed by ultrasonography. Similarly, higher baPWV, a mixed measure of both central and peripheral arterial stiffness, has been linked to preeclampsia/gestational hypertension

[22]. However, these studies have focused largely on European/Caucasian premenopausal women, and whether these associations persist in midlife has been understudied.

The Study of Women's Health Across the Nation (SWAN) provides a unique opportunity to examine the impact of reproductive characteristics on subclinical CVD burden in a multiethnic cohort of late midlife women. Accordingly, the purpose of this analysis was to examine associations between reproductive factors (e.g., age at menarche, age at first birth, gestational diabetes, gestational hypertension/preeclampsia) and several validated measures of subclinical CVD burden (i.e., carotid IMT and plaque, and baPWV) in late midlife women to determine how these factors may affect specific vascular beds. As a secondary aim, we examined the relationship of reproductive factors with a composite index of subclinical CVD that provides information on vascular remodeling and cumulative subclinical disease burden across multiple arterial sites [23]; there is accumulating evidence that subclinical markers of CVD may have an additive prognostic factor [24] and a similar index has been used in menopausal women [25]. Given the current evidence in premenopausal women, we hypothesized that earlier age at menarche, earlier age at first birth, greater parity, no or inconsistent breastfeeding (< 3 months), and adverse pregnancy outcomes (i.e., gestational hypertension/preeclampsia, gestational diabetes, preterm birth) are associated with greater subclinical CVD burden in late midlife women. Evaluating the association between reproductive factors and late midlife subclinical CVD may help identify important risk factors in women.

2. Materials and methods

2.1. Study participants

SWAN is a multiethnic cohort study designed to characterize the biological and psychosocial changes that occur during the menopausal transition. Details of the SWAN procedures and sampling frame have been reported [26]. Women were enrolled at one of seven research sites: Detroit, MI; Boston, MA; Chicago, IL; Oakland, CA; Los Angeles, CA; Newark, NJ; and Pittsburgh, PA. At enrollment (1996–1997), SWAN participants (n = 3302) were pre-menopausal or early perimenopausal women (a menstrual cycle in the past three months), age 42–52 years, with an intact uterus and at least one ovary, who menstruated in the preceding three months, were not pregnant or breast-feeding, and had not used oral contraceptives or hormone therapy within last three months of enrollment. Each study site enrolled non-Hispanic White women and one of four other predetermined racial/ethnic groups (Black women in Detroit, MI, Boston, MA, Chicago, IL, and Pittsburgh, PA; Japanese women in Los Angeles, CA; Chinese women in Oakland, CA; and Hispanic women in Newark, NJ). Participants were assessed through a standardized protocol at study entry and followed for approximately 21 years through 2018.

We included women who completed a reproductive history questionnaire at the 13th SWAN visit (2011–2012) and had a carotid ultrasound assessment and baPWV measure at visit 12 or 13. Six sites (all sites except Los Angeles) assessed subclinical CVD at visit 12 or 13. Of 2249 participants who completed a reproductive history questionnaire at visit 13, 1160 women had complete subclinical CVD data (i.e., carotid IMT, plaque, and baPWV). Because we were particularly interested in pregnancy features, nulliparous women were excluded

from this analysis (n = 196). Women with a history of myocardial infarction or stroke (n = 8) were included, but sensitivity analyses were performed (see Statistical Analyses). Thus, our final sample consisted of 964 women (Fig. 1). Written informed consent was obtained from each participant. The institutional review boards at each study site approved SWAN protocols.

2.2. Reproductive history

The exposure variables of interest were age at menarche, parity (number of births at ≥ 20 weeks gestation), age at first birth, consistent breastfeeding (≥ 3 months for each birth), preterm birth (delivery of any birth at < 37 weeks gestation), hypertensive disorders of pregnancy (i.e., gestational hypertension, preeclampsia), and gestational diabetes. Reproductive history was assessed using detailed interviewer-administered questionnaires. Information on age at menarche and breastfeeding duration for each birth was retrieved from the baseline SWAN visit. Parity, age at first birth, pregnancy complications (i.e., gestational hypertension, preeclampsia, gestational diabetes), and preterm birth were retrieved from data collected at the 13th SWAN visit. Interviews were conducted in the clinic/office, over the telephone, or in the respondent's home.

2.3. Subclinical CVD measures

Carotid ultrasound: Bilateral ultrasound carotid images were obtained using a Terason t3000 Ultrasound System (Teratech Corp, Burlington, MA) equipped with a variable frequency 5-12 Mhz linear array transducer, and were read centrally at the SWAN Ultrasound Reading Center (University of Pittsburgh Ultrasound Research Lab [URL]). Two digitized images were obtained of the distal common carotid artery (CCA), on each side, 1 cm proximal to the carotid bulb; one measurement was generated for each pixel over the area, for a total of approximately 140 measures for each segment. From each of these 4 images, using the Artery Measurement System (AMS) semi-automated edge detection software [27], IMT measures were obtained by electronically tracing and measuring the distance between the lumen-intima and the media-adventitia interfaces of the near and far walls of the CCA. The mean of the average readings of all 4 images were used in analyses.

The presence and extent of plaque was evaluated in each of 5 segments of the left and right carotid artery (distal and proximal CCA, carotid bulb, and proximal internal and external carotid arteries). Consistent with the Mannheim and ASE consensus statements [28], plaque was defined as a distinct area protruding into the vessel lumen that was at least 50% thicker than the adjacent IMT and summarized as the presence or absence of any plaque. Additionally, for each of the bilateral carotid segments, the degree of plaque was graded between 0 (no observable plaque) to 3 (plaque covering 50% or more of the vessel diameter). The grades from all segments of the combined left and right carotid artery were summed to create the plaque index (possible range:0-30) [29]. The plaque index was found to be a valid and reproducible measure of carotid atherosclerosis, within a number of populations [30]. Sonographers at each study site were trained by the University of Pittsburgh URL and monitored during the study period for reliability. Reproducibility was evaluated in 15–23 participants at each site; at each site the majority of scans were performed by one sonographer (100% at 4 sites and 91% at 1 site). The intra-class

correlation was 0.77 for site sonographers; for readers at the URL, the reading center for SWAN, intra-class correlation was > 0.90 for IMT intra- and inter-reads and 0.93 for plaque index assessment. These scanning and reading protocols have been used in prior studies [29,31,32].

baPWV: baPWV was measured using the VP2000 system (Omron Health Care Co., Kyoto, Japan), a non-invasive automated waveform analyzer. This device provides measures of baPWV, a mixed measure of central and peripheral PWV, on both right and left sides — average of the two sides was used for our study. baPWV is the distance in centimeters between the brachial and ankle arterial recording sites divided by the time delay in seconds between the foot of the respective waveforms. The distance or path length for brachial/ankle arterial sites was calculated based on a height-based algorithm [33]. The reproducibility of this measure is excellent, with intra and inter-technician correlation coefficients of > 0.93 for all sites.

2.4. CVD risk factors and other covariates

CVD risk factors were drawn from the SWAN visit concurrent with carotid ultrasound assessment and included body mass index (BMI, weight in kilograms divided by height in meters squared), systolic blood pressure, smoking (past, current/ever), and physical activity assessed using a modified Baecke Scores of Habitual Physical Activity. Systolic and diastolic blood pressure were manually measured twice at each SWAN visit by trained and centrally certified technicians. The two sequential BP values were averaged. At each visit, women were queried about current medication use including hypertension medications. Women were classified as diabetic by the carotid ultrasound visit (Visit 12 or 13) based on longitudinal fasting glucose data (≥ 126 mg/dL [≥ 7 mmol/L]) and use of insulin or anti-diabetic agents. Ever use of each of the following medications (anti-hypertensive, anti-diabetics, lipid-lowering) was based defined as yes if participants self-reported use at any study visit.

Blood was drawn in the morning following a 12-h fast. Samples were refrigerated prior to centrifugation 1-2 h after phlebotomy, and the serum was aliquotted, frozen (-80°C), and sent on dry ice to the University of Michigan. Serum measures of fasting insulin, glucose, and lipids were measured on a Siemens ADVIA 2400 automated chemistry analyzer utilizing Siemens ADVIA chemistry system reagents at the University of Michigan Pathology Laboratory, Ann Arbor, MI. Serum insulin was measured using radioimmunoassay. Serum glucose was measured using a two-step enzymatic reaction that utilizes hexokinase and glucose-6 phosphate dehydrogenase enzymes. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index was calculated as (fasting insulin (mU/Liter)* fasting glucose (mmoles/Liter/22.5) [34]. EDTA-treated plasma was used to determine lipid fractions. Triglycerides were analyzed by enzymatic methods on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) and high-density lipoprotein cholesterol (HDL-c) was isolated using heparin-2M manganese chloride [35]. Low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald equation [36]. In a subsample of women ($n = 561$, 59%), high-sensitivity C-reactive protein

(hsCRP) was quantitated from plasmas using an ultrasensitive rate immunonephelometric method (Dade-Berhing, Marburg Germain).

Demographic and socioeconomic characteristics including race/ethnicity and education (highest level of education: less than high school, some college/vocational training, college degree/post college) were assessed using interviewer-administered survey items at baseline as established by the SWAN Coordinating Center and reported previously [15,16,26]. Financial strain (how hard it was to pay for basics: very hard/somewhat hard, not hard at all) was self-reported annually and data from the visit corresponding to the carotid ultrasound assessment was used in this analysis. Menopause status was based on reports about frequency and regularity of menstrual bleeding and use of hormone therapy (premenopausal: bleeding in the last 3 months with no cycle irregularity in the previous 12 months; perimenopausal: bleeding in the last 3 months with some change in cycle regularity, or bleeding in past 3–12 months; natural postmenopausal: 12 months of no menses not due to bilateral oophorectomy; postmenopausal by bilateral oophorectomy: 12 months of no menses following surgical removal of the ovaries; and unknown: hormone therapy or other circumstance interfering with ability to characterize bleeding patterns) [37].

2.5. Statistical analyses

Reproductive factors and individual subclinical CVD measures: All analyses were conducted using SAS 9.3 (SAS Institute, Cary, North Carolina, USA). Descriptive statistics were used to summarize variables, as well as detect outliers and missing values. Normality of the distribution was examined with a normal probability plot, when applicable. Reproductive factors that have been associated with CVD in the literature (e.g., age at menarche, gestational hypertension/preeclampsia, gestational diabetes) [3,38] were entered separately into bivariate linear (for IMT and baPWV) and logistic (for plaque) regression analyses to evaluate the independent impact of each reproductive factor on subclinical CVD. Next, reproductive factors associated with any of the subclinical CVD measures at $p < 0.1$ were entered simultaneously to evaluate the independent impact of each reproductive factors on individual subclinical CVD measures. Models were adjusted for covariates associated with the reproductive factors and our outcomes of interest at $p < 0.05$; for example, we adjusted for HDL-C instead of LDL-C because HDL-C, and not LDL-C, was associated with both our independent and dependent variables. We first adjusted for age at carotid scan, race/ethnicity, education, financial strain, and study site. Final models were adjusted for all CVD risk factors from the concurrent visit at which carotid assessment was performed (BMI, smoking, systolic blood pressure, HOMA-IR, HDL-C) and medications (blood pressure, diabetes, anti-lipidemic). In addition, to better understand the contribution of potential pathway factors to the tested associations, we created separate models adjusting for HDL-C, HOMA-IR, and systolic blood pressure one at a time; we additionally adjusted for hsCRP in a subsample of women with the measure (Supplementary Tables 1 and 2).

Reproductive factors and composite subclinical CVD: As in previous studies of subclinical CVD [25,29,39], a composite index was created using the aforementioned subclinical measures (i.e., carotid IMT, plaque, and baPWV). An approximate 75th percentile cut point according to the distribution of the current study population data was

used to divide each measure into “0” (low subclinical CVD) or “1” (high subclinical CVD). High levels of each measure were defined as follows: baPWV greater than 1376.4 cm/s (> 75th percentile), carotid IMT greater than 0.87 mm (> 75th percentile), carotid plaque index ≥ 2 . These three dichotomous variables were summed, with the composite subclinical CVD index ranging from “0” (low subclinical CVD) to “3” (high subclinical CVD). Since only 37 women (4%) had a composite index of “3”, this group was combined with women who had a composite index of “2”. Thus, our composite subclinical CVD index consisted of three groups: “low” (subclinical CVD = 0, n = 462), “medium” (subclinical CVD = 1, n = 330), and “high” (subclinical CVD ≥ 2 , n = 172).

Multinomial logistic regression was used to model the subclinical CVD index groups; ordinal logistic regression was not performed because the required proportional odds assumption was not met. Reproductive factors were entered simultaneously into multinomial logistic regression models. Models were adjusted for socio-demographic factors and CVD risk factors as described earlier.

Model fit and sensitivity: We tested interactions with race/ethnicity in all analyses and stratified by race/ethnicity when an interaction was detected. We performed sensitivity analyses in models by excluding: 1) women with a history of CVD events; 2) women with multiple adverse pregnancy outcomes; and 3) women with multiple births (e.g., twins) (Supplementary Table 3). Model analyses were performed to verify all model assumptions and examine for multicollinearity. If a variable had a variance inflation factor ≥ 10 , we examined its correlation with other variables and removed covariates that were highly correlated (≥ 0.7) to other variables.

3. Results

3.1. Participant characteristics

This analysis included 964 parous women (46% White, 37% Black, 6% Hispanic, 11% Chinese). Participant characteristics at the SWAN visit corresponding to carotid ultrasound assessment (visit 12/13) are presented in Table 1. Women were on average age 60.2 ± 2.7 years (mean $\pm$ standard deviation) at subclinical CVD assessment, had some college education (51%), and 95% were postmenopausal. In terms of reproductive factors, 11% of women reported ever having gestational hypertension/preeclampsia, 5% had a history of gestational diabetes, and 14% reported a prior preterm birth. Mean systolic BP was 122.8 ± 17.2 mmHg and 41% of women reported use of anti-hypertensive medications. There were 462 (48%) women with a low composite subclinical CVD index ($\leq$ 75th percentile for all three subclinical measures), 330 (34%) with a medium composite subclinical CVD index (> 75th percentile for one measure), and 172 (18%) with a high composite subclinical CVD index (> 75th percentile for two to three measures). Of women with a medium subclinical CVD index, 35% had a baPWV above the 75th percentile, 31% had IMT above the 75th percentile, and 35% had a plaque index ≥ 2 . Women with a high subclinical CVD index were more likely to have baPWV and IMT > 75th percentile (73% and 85%, respectively).

3.2. Associations between reproductive factors and individual subclinical CVD measures

Tables 2 and 3 present results for the associations between reproductive characteristics and the individual subclinical CVD measures. Since bivariate analyses showed that all our reproductive factors were associated with at least one of the subclinical CVD measures at $p < 0.1$ (Table 2), all reproductive factors were entered into our adjusted models examining individual subclinical CVD measures and composite measures (Table 3). In our models adjusting for socio-demographics (age, study site, education, financial strain, race/ethnicity), older age at first birth was associated with lower carotid IMT ($\beta: -0.003$, $p = 0.0003$) and baPWV ($\beta: -4.0$, $p = 0.002$); this association was attenuated when adjusted for CVD risk factors (IMT $\beta: -0.001$, $p = 0.09$; baPWV $\beta: -0.9$, $p = 0.47$). History of gestational hypertension/preeclampsia was associated with higher carotid IMT, but not with baPWV (Table 3). In final models for IMT, gestational hypertension/preeclampsia was associated with a 0.038 mm thicker carotid IMT ($p = 0.004$) compared to history of all normotensive pregnancies. History of gestational hypertension/preeclampsia was also associated with greater carotid plaque index (OR: 1.75; 95% CI: 1.03, 2.98). History of gestational diabetes was associated with higher baPWV in fully-adjusted models ($\beta = 64.8$, $p = 0.03$). Supplementary Tables 1 and 2 show that in a subsample of participants with hsCRP measures, gestational hypertension/preeclampsia was still associated with IMT after adjusting for hsCRP (IMT $\beta = 0.059$, $p = 0.001$), and gestational diabetes remained associated with baPWV ($\beta = 76.8$, $p = 0.04$). In terms of interactions with race/ethnicity, we found that history of preterm birth was associated with lower carotid IMT among Black women ($\beta: -0.5$, $p = 0.02$), but not White women ($\beta: 0.01$, $p = 0.47$). There were no other interactions with race/ethnicity.

3.3. Associations between reproductive factors and composite subclinical CVD

Our analyses of the composite subclinical CVD index revealed that history of gestational hypertension/preeclampsia was associated with a high subclinical CVD burden (Table 4). In our initial models (adjusting for age, study site, education, financial strain, race/ethnicity, and parity), older age at first birth was associated with lower odds of a high composite subclinical CVD index (OR: 0.95; 95% CI: 0.92, 0.99), but not when adjusted for CVD risk factors ($p = 0.39$). In fully-adjusted models, history of gestational hypertension/preeclampsia remained associated with a high subclinical CVD burden (OR: 2.19; 95% CI: 1.17, 4.09). Though significant in models of baPWV, history of gestational diabetes was not associated with our composite subclinical CVD index.

4. Discussion

This study was the first to investigate the relation between pregnancy-related factors and multiple measures of subclinical CVD, which may provide information on vascular health in multiple vascular beds. Among late midlife women in SWAN, we found that earlier age at first birth is associated with measures of arterial remodeling and stiffness, but this association may be explained by traditional cardiovascular risk factors. History of gestational hypertension/preeclampsia, on the other hand, is associated with greater carotid plaque, a direct measure of atherosclerosis, independently of traditional CVD risk factors.

Interestingly, while history of gestational hypertension/preeclampsia was associated with carotid IMT and plaque, gestational diabetes was associated with baPWV.

In the Women's Health Initiative Observational study, earlier age at first birth was related to later life CVD in postmenopausal women [40]. In this analysis, any association between age at first birth and subclinical CVD was attenuated after adjusting for CVD risk factors, suggesting that there is no alternative pathway linking age at first birth to subclinical CVD. This is consistent with studies showing that age at first birth is not associated with CVD after adjustment for socio-economic status and CVD risk factors [41]. A possible explanation for associations between age at first birth and CVD in minimally adjusted models is that an earlier age at first birth is related to social factors that are also associated with greater CVD risk (e.g., early life financial hardship, lower educational attainment, smoking) [42]. This is supported by a recent analysis in the British birth cohort that showed a significant association between age at first birth and CVD risk factors in both men and women [43], further indicating a non-biological link between age at first birth and CVD. These observations, together with our current findings, support the need for interventions that target social and behavioral factors related to earlier age at first birth and CVD risk.

Consistent with a previous analysis of preterm birth, blood pressure, and subclinical CVD [15], we found an interaction between preterm birth and race/ethnicity in relation to carotid IMT. A prior preterm birth was associated with lower IMT in Black women, but not in White women. Earlier analyses have shown that anti-hypertensive treatment is associated with lower carotid IMT [44]. We found that Black women were more likely to report a preterm birth and anti-hypertensive use, potentially explaining our observed racial/ethnic differences. Furthermore, excluding women with prevalent hypertension and anti-hypertensive medications, attenuated the negative association between preterm birth and IMT. Due to small sample sizes of Hispanic and Chinese women, we could not examine the associations separately in these groups.

Gestational hypertension and preeclampsia, which affect 2-8% of pregnancies worldwide [45], are well-established risk factors for incident hypertension and later life CVD [46]. Our analysis found that CVD risk factors might not fully explain the relationship between hypertensive pregnancy disorders and greater maternal carotid IMT and plaque in late midlife. A 0.06 mm IMT difference (Table 3) between women with a history of gestational hypertension/preeclampsia versus those without, is similar to IMT progression over 7–8 years in midlife [16,47]. Based on observational studies an absolute IMT difference of 0.1 mm corresponds to a 10-15% increase in future risk of myocardial infarction and 13-18% future risk of stroke [48]. Our results are consistent with prior analyses that found a greater carotid IMT among midlife women with a history of preeclampsia compared to women with normotensive pregnancies [49]. However, while a previous study reported an association with arterial stiffness [50], we did not find a significant relationship between hypertensive pregnancy disorders and baPWV. One potential explanation for this discrepancy is that we assessed arterial stiffness using baPWV, a mixed measure of central and peripheral stiffness, and the prior analysis used carotid-femoral PWV. Though baPWV is an independent predictor of CVD, [19], carotid-femoral PWV has been shown to be a more robust measure in evaluating cardiovascular complications in patients with essential hypertension [51]. It is

also important to note that history of gestational hypertension/preeclampsia was assessed by self-report, which has low to moderate sensitivity and may underestimate the number of women with a history of a hypertensive pregnancy disorder [52]. Nonetheless, our findings suggest that an alternative pathway exists linking gestational hypertension/preeclampsia to atherosclerotic measures (i.e., carotid IMT and plaque) that is not mediated by traditional CVD risk factors. Though it has been postulated that one such pathway may be an inflammatory response, we found that gestational hypertension/preeclampsia was still associated with IMT after adjusting for hsCRP. Recent studies have observed increases in inflammatory factors during preeclampsia [53], which have also been associated with atherosclerosis [54]. The role of inflammation in associations between hypertensive pregnancy disorders and subclinical CVD in midlife women warrants additional study.

History of gestational diabetes was not associated with our composite subclinical CVD index, though it was associated with baPWV. Our 80.0 cm/s baPWV difference between women with a history of gestational diabetes versus those without is clinically relevant given that an increase of 100 cm/s of baPWV has been associated with a 12% increase in the risk of CVD [55]. These findings are consistent with two analyses in younger women (up to 5 years postpartum) that showed increased arterial stiffness among women with gestational diabetes [56,57]. Importantly, increased arterial stiffness has been associated with hormonal and metabolic alterations, particularly insulin resistance [58,59]. Studies have shown arterial stiffening across all age groups in patients with diabetes and metabolic syndrome [60]. Contrary to our analysis, in a previous study up to 20 years post-partum women with a history of gestational diabetes had greater carotid IMT than women without a history of gestational diabetes [14]. However, this study was conducted among premenopausal women and whether associations between gestational diabetes and subclinical CVD persist in postmenopause, when women experience adverse cardiometabolic changes (obesity, dyslipidemia, insulin resistance) [61,62], have not been assessed. In addition, our analysis may be limited by the small sample of women with a history of gestational diabetes.

4.1. Limitations and strengths

There are several limitations to consider in this analysis. First, since pregnancy-related data were collected retrospectively, recall bias may limit the internal validity of these findings. Previous studies have shown that maternal recall of preeclampsia has a low sensitivity (71%) and high specificity (93%) [51]. Though maternal recall of gestational diabetes is more accurate, this analysis may be limited by the small sample size of women with reported history of gestational diabetes. Furthermore, the relatively modest sample size overall, and the modest frequency of some of the reproductive exposures may have limited the ability to detect more subtle associations. It is also important to note that our composite index of subclinical CVD was limited to carotid IMT, plaque, and baPWV because we did not have additional measures previously included in similar indices (e.g., coronary artery calcification).

A key strength of our study is the multiethnic sample of postmenopausal women with well-characterized subclinical CVD measures, including baPWV as well as carotid IMT and plaque. Moreover, we were able to account for important socioeconomic and cardiovascular

risk factors, such as education, financial strain, smoking, blood pressure, lipid profile, and HOMA-IR. Another strength of this analysis was the availability of early to midlife reproductive factors, which allowed us to evaluate the association between several reproductive factors across a woman's life course with subclinical CVD in late midlife.

4.2. Conclusions

In this analysis we show that among late midlife women, a history of gestational hypertension/preeclampsia is independently associated with greater subclinical CVD burden. Earlier age at first birth may be associated with future CVD, but not when accounting for traditional CVD risk factors. We further show that while history of gestational hypertension/preeclampsia is related to subclinical atherosclerosis (carotid IMT and plaque), history of gestational diabetes may be associated with arterial stiffness (baPWV). These findings suggest that pregnancy history is an important marker of CVD risk in late midlife and may impact the vasculature through distinct pathways. Future studies are necessary in other populations are necessary to further evaluate our findings. Additional studies examining associations between adverse pregnancy outcomes and individual cardiovascular risk factors in late midlife women (e.g., blood pressure) may be useful to detect more subtle associations. Analyses are also necessary to assess the benefit of a composite subclinical CVD index for earlier CVD risk modification in midlife women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- We identified sex-specific factors associated with subclinical CVD measures in late midlife women.
- Hypertension in pregnancy was related to midlife subclinical atherosclerosis.
- History of gestational diabetes was associated with arterial stiffness in midlife.
- Need to assess benefit of a composite subclinical CVD index for risk modification.

Fig. 1.

Population included in the analyses.

*Five sites completed carotid ultrasound and pulse wave velocity assessment: Detroit, MI; Oakland, CA; Pittsburgh, PA; Chicago, IL; and Newark, NJ

Table 1

Participant characteristics at SWAN Visit 12/13 (n = 964).

Maternal characteristics	N	Mean $\pm$ SD, median [IQR], or %
Demographics		
Age (years)	964	60.2 $\pm$ 2.7
Race/Ethnicity		
White	445	46.3
Black	351	36.5
Hispanic	62	6.4
Chinese	104	10.8
Education		
< High school	70	7.3
Some college/vocational training	494	51.2
College degree/post college	400	41.5
Somewhat/very hard paying for basics	354	37.0
CVD risk factors and subclinical CVD measures		
Body mass index (kg/m ²)	952	30.2 $\pm$ 7.2
Current/Ever smoker	113	11.8
Physical activity score	916	7.6 $\pm$ 1.8
Systolic blood pressure (mm/Hg)	957	122.8 $\pm$ 17.2
Diastolic blood pressure (mm/Hg)	957	74.3 $\pm$ 9.6
<i>b</i> ₁ Triglyceride (mg/dL)	956	99 [75, 138]
<i>b</i> ₁ LDL-C (mg/dL)	956	123.7 $\pm$ 34.1
<i>b</i> ₁ HDL-C (mg/dL)	960	62.0 $\pm$ 16.2
HOMA	909	2.2 [1.3, 3.9]
hsCRP (mg/L)	571	3.2 [1.2, 7.3]
Medications		
Anti-hypertensives	390	40.9
Anti-diabetics	107	11.2
Lipid-lowering	281	31.3

Maternal characteristics	N	Mean $\pm$ SD, median [IQR], or %
Anticoagulant	6	0.6
History of CVD (heart attack, stroke)	8	0.82
Common carotid IMT (mm)	964	0.80 $\pm$ 0.12
baPWV (cm/s)	964	1239 $\pm$ 214
Carotid plaque index		
0	555	57.5
1	180	18.7
2	229	23.8
Composite subclinical CVD index		
Low	462	48
Medium	330	34
High	172	18
Reproductive		
Age at menarche (years)	964	12.5 $\pm$ 1.7
Early menarche (age 12 years)	506	52.5
Parity (number of live births, continuous)	964	2.5 $\pm$ 1.2
Parity (number of live births, categorical)		
1	192	19.9
2	380	39.4
3	392	40.7
Age at first birth (years)	964	24.9 $\pm$ 6.1
Age at last birth (years)	964	30.5 $\pm$ 6.0
Gestational HTN/Preeclampsia	104	10.8
Gestational diabetes	50	5.2
Preterm birth	131	13.6
Multiple adverse pregnancy outcomes ^a	19	2.0
Consistent breastfeeding (3 months)	91	9.4
Menopause status		
Premenopausal/Unknown	33	3.4
Perimenopausal	19	2.0
Natural postmenopause	840	87.1

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Maternal characteristics	N	Mean ± SD, median [IQR], or %
Postmenopausal by bilateral oophorectomy	77	8.4
Age at final menstrual period	602	52.0 ± 2.9
Reproductive duration	617	39.5 ± 3.3
Hormone therapy use ever	363	37.9

baPWV = brachial-ankle pulse wave velocity, CVD = cardiovascular disease, HOMA = homeostatic model assessment, HTN = hypertension, IMT = intima-media thickness, SCVD = subclinical cardiovascular disease.

Values reported are mean ± standard deviation, median [interquartile range], or sample size (%).

^a A history of more than one adverse pregnancy outcome including gestational hypertension/preeclampsia, gestational diabetes, and preterm birth (recurrent outcome, or a combination of these).

^b Values in mmol/L: Triglyceride = 5.5 [4.2, 7.7], LDL-C = 6.8 ± 1.9, HDL-C = 3.4 ± 0.9, hsCRP = 30.5 [11.4, 69.5].

Table 2
Bivariate associations between individual reproductive characteristics and subclinical CVD measures.

	CCA IMT (mm)		baPWV (cm/s)		Plaque Index 2	
	β (SE)	<i>p</i>	β (SE)	<i>p</i>	OR (95% CI)	<i>p</i>
Age at menarche	0.001 (0.002)	0.52	7.5 (4.1)	0.06	0.93 (0.85, 1.02)	0.11
Parity (number of births)	0.002 (0.003)	0.48	17.6 (5.7)	0.002	0.99 (0.87, 1.13)	0.93
Age at first birth	-0.003 (0.001)	< 0.0001	-6.0 (1.1)	< 0.0001	0.99 (0.96, 1.01)	0.26
Gestational HTN/preeclampsia	0.054 (0.013)	< 0.0001	48.1 (22.2)	0.03	1.91 (1.20, 3.04)	0.007
Gestational diabetes	0.016 (0.018)	0.36	72.2 (31.1)	0.02	1.18 (0.60, 2.32)	0.64
Preterm birth	-0.005 (0.012)	0.64	51.2 (20.1)	0.01	1.09 (0.70, 1.70)	0.69
Consistent breastfeeding (> 3 months)	0.002 (0.013)	0.90	-40.4 (23.6)	0.09	0.92 (0.54, 1.56)	0.75

baPWV = brachial-artery pulse wave velocity, CCA IMT = common carotid artery intima-media thickness, HTN = hypertension.

Table 3

Associations between reproductive characteristics (modeled simultaneously) and individual subclinical CVD measures.

	CCA IMT (mm)		baPWV (cm/s)		Plaque Index 2	
	β (SE)	<i>p</i>	β (SE)	<i>p</i>	OR (95% CI)	<i>p</i>
Model 1						
Age at menarche	0.001 (0.002)	0.69	6.8 (4.0)	0.09	0.92 (0.84, 1.01)	0.09
Parity (number of births)	-0.006 (0.004)	0.11	5.2 (6.3)	0.41	0.94 (0.81, 1.09)	0.43
Age at first birth	-0.003 (0.001)	0.0003	-4.0 (1.3)	0.002	0.99 (0.97, 1.03)	0.94
Gestational HTN/preeclampsia	0.06 (0.013)	< 0.0001	40.0 (22.4)	0.08	2.00 (1.22, 3.28)	0.006
Gestational diabetes	0.017 (0.018)	0.35	86.3 (31.4)	0.006	1.11 (0.54, 2.30)	0.77
Preterm birth ^b	-0.014 (0.012)	0.23	33.0 (20.2)	0.10	1.09 (0.69, 1.73)	0.71
Consistent breastfeeding (< 3 months)	0.012 (0.013)	0.37	-9.9 (23.4)	0.67	0.97 (0.56, 1.69)	0.92
Model 2 ^a						
Age at menarche	0.0003 (0.002)	0.88	5.5 (3.6)	0.12	0.95 (0.86, 1.05)	0.28
Parity (number of births)	-0.004 (0.004)	0.31	10.0 (5.8)	0.09	0.96 (0.82, 1.12)	0.59
Age at first birth	-0.001 (0.001)	0.09	-0.9 (1.2)	0.47	1.01 (0.98, 1.04)	0.53
Gestational HTN/preeclampsia	0.038 (0.013)	0.004	-4.4 (21.1)	0.84	1.75 (1.03, 2.98)	0.04
Gestational diabetes	0.009 (0.018)	0.59	64.8 (29.0)	0.03	1.01 (0.47, 2.20)	0.98
Preterm birth ^b	-0.023 (0.012)	0.05	-2.4 (18.8)	0.90	0.82 (0.46, 1.44)	0.69
Consistent breastfeeding (< 3 months)	0.02 (0.013)	0.13	6.3 (21.1)	0.77	0.97 (0.55, 1.73)	0.93

baPWV = brachial-artery pulse wave velocity, CCA IMT = common carotid artery intima-media thickness.

Model 1 = Age at carotid scan, race/ethnicity, site, education, financial strain.

Model 2 = Model 1 + BMI, smoking, HOMA, HDL-C, systolic blood pressure, physical activity.

^a Adjustment for medications (anti-hypertensives, anti-diabetics, lipid-lowering) did not alter estimates by 10%.

^b Interaction with race/ethnicity (White, Black/African-American). This was significant among Black women, but not White Women.

Table 4

Associations between reproductive characteristics (modeled simultaneously) and composite subclinical CVD index.

	SCVD = 1		SCVD = 2	
	OR (95% CI)	p	OR (95% CI)	p
Model 1				
Age at menarche	1.07 (0.98, 1.16)	0.14	1.02 (0.91, 1.13)	0.76
Parity (number of births)	1.11 (0.97, 1.27)	0.14	0.96 (0.81, 1.14)	0.64
Age at first birth	1.00 (0.97, 1.03)	0.96	0.95 (0.92, 0.99)	0.006
Gestational HTN/preeclampsia	1.37 (0.81, 2.31)	0.24	2.97 (1.71, 5.17)	0.0001
Gestational diabetes	0.61 (0.28, 1.34)	0.22	1.80 (0.85, 3.82)	0.12
Preterm birth	1.00 (0.65, 1.55)	0.99	0.80 (0.45, 1.40)	0.43
Consistent breastfeeding (3 months)	0.94 (0.56, 1.56)	0.80	1.01 (0.52, 1.96)	0.98
Model 2^{a,b}				
Age at menarche	1.04 (0.94, 1.14)	0.47	1.03 (0.92, 1.16)	0.59
Parity (number of births)	1.15 (0.99, 1.33)	0.07	1.02 (0.84, 1.23)	0.87
Age at first birth	1.02 (0.99, 1.06)	0.16	0.98 (0.94, 1.02)	0.39
Gestational HTN/preeclampsia	1.18 (0.67, 2.08)	0.56	2.19 (1.17, 4.09)	0.01
Gestational diabetes	0.49 (0.21, 1.16)	0.10	1.40 (0.59, 3.32)	0.45
Preterm birth	0.76 (0.47, 1.23)	0.26	0.56 (0.29, 1.05)	0.07
Consistent breastfeeding (3 months)	1.02 (0.60, 1.76)	0.94	1.22 (0.60, 2.49)	0.59

SCVD = subclinical cardiovascular disease. Reference category = 0.

Model 1 = Age at carotid scan, race/ethnicity, site, education, financial strain.

Model 2 = Model 1 + BMI, smoking, HOMA, HDL-C, systolic blood pressure, physical activity.

^a Adjustment for medications (anti-hypertensives, anti-diabetics, lipid-lowering) did not alter estimates by 10%.

^b No interactions with race/ethnicity (White, Black/African-American).