Original Article

Assessment of Cardiovascular Risk in Natural and Surgical Menopause

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Abstract

Background: Menopause is associated with increased cardiovascular disease (CVD) risk. Arterial stiffness, a biomarker of vascular aging, increases the risk for CVD. **Aims and Objectives:** The study was aimed to determine whether menopause is associated with arterial stiffness amongst natural and surgical menopausal women. **Materials and Methods:** We conducted a cross-sectional study amongst natural postmenopausal women, with Surgical menopause and Premenopausal. Arterial stiffness was measured by Periscopy TM. Large artery stiffness may be an important mechanism by which hysterectomy increases the risk of cardiovascular disease in postmenopausal women. **Results:** Carotid femoral pulse wave velocity (cfPWV) and Brachial Ankle Pulse wave velocity (baPWV) were significantly higher in surgical and natural menopause compared to women with Premenopausal group.

Keywords: Cardiovascular risk, periscopy, pulse wave velocity, surgical menopause

Introduction

Cardiovascular risk factors among women entering the menopause are inadequately managed as clinicians often fall short to recognize risk factors.[1] Hysterectomy for benign indications is one of the most common surgical procedures in women, but the association between the procedure and cardiovascular disease (CVD) is not entirely understood.[2,3]

Menopause is strengthening the association between C-reactive protein and pulse wave velocity (PWV) independent of age. It is likely that menopause is associated with an increase in inflammation, which in turn results in increased stiffening of the vasculature and increased risk of cardiovascular outcomes.[4] Naturally, postmenopausal (NMP) women had lower systolic blood pressure levels across a large age range than premenopausal (PrMP), or surgical postmenopausal (SMP) women.[5]

The prevalence of CVD increases with advancing age in both women and men, with premenopausal women having a lower prevalence compared with age-matched men until around the time of the menopause transition, where thereafter, women have an equal or greater prevalence of CVD.[6]

Menopause and hormone replacement therapy influence the cardiovascular risk factors. The oral-estrogen leads to significant decrease of low-density lipoprotein cholesterol (LDL-), and significant increase of high-density lipoprotein (HDL) and triglyceride (TG) plasma levels.[7] This female cardioprotective advantage has often been attributed to the effects of estrogen before menopause which is then lost when ovarian function declines with menopause. Indeed, early menopause, including hysterectomy with ovarian preservation or with oophorectomy has been reported to be a significant predictor of CVD.[2,8] The CVD risk associated with hysterectomy itself (with intact ovaries) has been attributed to early menopause related to premature ovarian failure from disruption of ovarian blood flow.[2,9] However, a substudy of the Women's Health Initiative (WHI) placebo-controlled trial of conjugated equine estrogens revealed that hysterectomy (including bilateral or unilateral oophorectomy) without a history of hormonal replacement therapy (HRT) was associated with subclinical coronary artery disease independent of traditional CVD risk factors.[10] Moreover, among women with bilateral oophorectomy, HRT use within 5 years of

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surgery was associated with a lower prevalence of subclinical atherosclerosis.[10] These findings are consistent with the idea that estrogen deficiency associated with hysterectomy is related to the development of CVD. As hysterectomy is the second most common gynecological surgical intervention among women throughout the world, full understanding of physiological means behind its connection to increased CVD risk is of clinical significance.[11]

Large and medium artery stiffness, a marker of vascular aging, is a predictor of cardiovascular events.[12] In women after natural and surgical menopause, the vascular aging process appears to be accelerated, may be due to estrogen deficiency.

Propagation of blood through the arteries occurs during single heart systole. Transfer of kinetic energy by flowing blood through the stretched wall of the arteries made the physiological basis of consequent changes in pressure, flow, and PWV. PWV analysis determines if the vascular system is working properly, without any limitations that may produce health risks. Arterial stiffness caused by medial calcification and loss of elasticity is a very important factor leading to an increase in PWV. PWV is an effective and reproducible tool for evaluating vascular endothelial dysfunction and arterial stiffness. PWV Analysis is highly effective at estimating arterial stiffness. The arterial stiffness is proportionate to the speed of pulse wave. The augmentation index and central blood pressure data derived from this measurement are both recognized indicators of large artery stiffness.

In fact, arterial stiffness is greater in postmenopausal women compared to age-matched premenopausal women and lower in postmenopausal women using HRT compared to women not using HRT.[12-14] In the present study, we assessed the arterial stiffness in natural and surgical menopause females.

Methods

The study was commenced after obtaining approval from the Institutional Ethics Committee and written informed consent from the participants. The participants were recruited from Menopause clinic of the Department of Obstetrics and Gynecology. The study participants were send to a Central research laboratory for the assessment of hematological, biochemical profile, and periscopy.

The study was carried out in three groups:
1. Pre-menopausal group (PrMP, $n = 32$)
2. Natural menopausal group (NMP, $n = 64$)
3. Surgical menopausal group (SMP, $n = 31$).

Healthy postmenopausal women (between 48 and 65 years of age) who were estrogen-deficient (no use of HRT for at least 6 months) and did not have menses for at least 1 year were included in the study group, natural menopause category. Thirty-one women with a history of hysterectomy with bilateral oophorectomy and no use of HRT for at least 6 months were included in the category of surgical menopause. Thirty-two women with a history of the regular menstrual cycle, without any major medical or surgical illnesses, were included in the premenopausal group.

Age at menopause, postmenopause duration, prior HRT use, and parity were obtained from the medical history and physical examination. Menopausal status was assigned using self-reported menstrual cycle histories. Premenopausal status was defined as having a menstrual period in the past 3 months with no change in cycle regularity in the past 12 months. Postmenopausal status was defined as not having a menstrual period in the past 12 months. The duration of menopause was estimated from the self-reported onset of natural menopause and self-reported surgery date in those who had a hysterectomy with bilateral oophorectomy. Women were normotensive, nonsmokers, not taking any cardiovascular or lipid-lowering medications, and free of overt chronic diseases as assessed using medical history, physical examination, standard biochemical, and hematological evaluation.

Information about lifestyle factors such as the age of the participants, height and weight measurements were obtained from all the participants. Weight was measured using a digital portable scale. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Liver function test, renal function test, and complete blood count were assessed in all the study population.

Main periscopic parameters under study were ankle brachial index (ABI), arterial stiffness index (ASI), carotid-femoral PWV (cfPWV) pulse-wave velocity, brachial-ankle PWV (baPWV), ABI, central pressures, and augmentation index. These parameters were assessed using a noninvasive PC based arterial health assessment. Procedure to assess arterial properties by PeriScope™: Analysis system (PeriScope™, RMS Chandigarh). It is a PC based cardiovascular cnalysis cystem that uses simultaneous noninvasive blood pressure measurements from four limbs and ECG waveform to calculate important parameters such as PWV, ASI, ABI, and central aortic pressure values and ejection slope.[15] The patient in the supine position is attached with four limb BP cuffs and a 4 lead electrocardiography (ECG) cable to the periscope hardware. After entering all the patient details such as age, sex, weight, the height the test is started. This test is completely automatic. In the first run, all the 4 cuffs inflate and deflate recording the systolic/diastolic blood pressures and mean arterial pressure. After a brief pause, the second run starts during which the blood pressure oscillations are recorded simultaneously for all the 4 limbs along with the ECG waveforms. The total time required is about 10 min for the complete procedure including attachment of sensors. Using these waveforms, various parameters such as PWV, ABI, and ASI nomograms are calculated. All the results are displayed simultaneously on the screen. The software also has a unique quality control to validate the conducted test. It helps to reconduct the test properly if the consistency in the acquired waveform is not enough to calculate accurate results.

The on-screen analysis consists of all the acquired waveforms, PWVs, BP values, ABI values, graphical interpretive representation of the results, tabular representation of parameters, observed and normal values and their significance. This analysis gives a comprehensive diagnostic picture of the patient's cardiovascular status at a single glance.

Fasting plasma concentrations of glucose, TGs, total cholesterol (TC), LDL-C and HDL-cholesterol were determined using modular P-800 fully Automatic Biochemistry Analyser (Roche Diagnostics, USA). Analysis of serum TC, and TGs was performed on blood specimens collected by venipuncture and stored in EDTA-containing tubes. Blood sample collected for lipid profile testing was done after 12-h fasting.

Statistical analysis

One-way ANOVA was applied to assess differences in all the three groups variables for general characteristics of the study participants, lipid profiles, central aortic pressure pulse profile, and variables of arterial stiffness measurements (cfPWV, baPWV, ABI). Dunnett T3 multiple comparisons were applied to find the mean difference of variables and its correlation between the three groups and its level of significance. Data are presented as a mean ± standard deviation, and significant level was set at $P < 0.05$. Data analysis was performed with SPSS software, version 14.0 (SPSS Software Inc., Chicago, IL, USA).

Observation and Results

The physical and laboratory characteristics of the study participants are stratified in Table 1. This cross-sectional observational study was conducted among natural postmenopausal women ($n = 64$; age (years) - 58.2 ± 3.1), women with surgical menopause ($n = 31$; 54.2 ± 4.2) and premenopause ($n = 32$; 37.09 ± 5.8). Time since menopause was longer and age at menopause was less in women with surgical menopause compared to women with natural menopause. Hysterectomy with bilateral oophorectomy was performed at younger age group [all $P < 0.005$, Table 1]. Systolic and diastolic blood pressure was within normal limits in all the three study participants. However, it was significantly higher in natural menopause group compared to premenopausal and surgical menopause group [$P < 0.05$, Table 1]. TC and TGs were significantly higher among natural and surgically menopausal women compared to premenopausal group [$P < 0.05$ and 0.005, respectively, Table 1]. TC and TGs were significantly higher among surgical menopausal women compared to natural menopausal group [$P < 0.05$, Table 1]. HDL Cholesterol was significantly lower in the surgical menopausal group compared to premenopause and natural menopause group [$P < 0.05$, Table 1]. Central aortic systolic and diastolic blood pressures were within normal limits amongst all the study participants; however, it was significantly higher among NMP group compared to SMP and PrMP [$P < 0.05$, Table 2].

Central aortic pulse pressure was also within normal limit in all the study participants, but it was higher in surgical menopause group compared to natural menopause group [$P < 0.05$, Table 2]. Central aortic augmentation pressure (AoAugP) was significantly higher in NMP group compared to PrMP group [$P < 0.005$, Table 2]. AoAugP was lower in SMP group compared to NMP [$P < 0.05$, Table 2], but it was significantly higher compared to PrMP [$P < 0.05$, Table 2]. When we analyzed and compared the parameters of arterial properties we observed that cfPWW and baPWW were found to be significantly higher in NMP and SMP groups when compared to the PrMP group [$P < 0.05$, Table 2]. On comparing baPWW between NMP and SMP groups, no significant difference was observed. ABI was higher among both the menopause groups, but it was not significant [Table 2].

Discussion

Surgical menopause is associated with a greater degree of coronary atherosclerosis, calcified plaque, and increased CVD events.[2,9] We observed a decrease in endogenous estrogen deranged serum lipids, decreases carotid artery blood flow, and accelerated sub-clinical atherosclerosis as assessed noninvasively by cfPWV and baPWV. The interesting finding of this study is that postmenopausal women whether surgical or natural menopause have stiffer large elastic arteries compared to premenopausal women.

Table 1: Physical and biochemical parameters of the study participants

Dependent variable	NMP ($n=64$)	PrMP ($n=32$)	SMP ($n=31$)	*P*	Intergroup comparison (*P*)
Age	58.2±3.14	37.09±5.77	54.2±4.21	<0.0001	<0.0001*,†,‡
Age at menopause (years)	51.95±1.14	-	41.48±3.6	<0.0001	
Menopause duration, (years)	6.31±2.9	-	12.7±4.6	<0.0001	
BMI, kg/m^2	24.3±4.6	24.9±2.2	24.6±4.3	>0.05	NS
Resting HR, bpm	70.6±18.5	69.7±11.8	72.3±16.5	>0.05	NS*,†,‡
Total cholesterol, (mg/dl)	192.94±30.26	179.88±27.94	198.61±26.77	>0.05	NS*,† <0.05‡
LDL cholesterol (mg/dl)	142.97±22.97	128.91±21.6	141.87±21.9	<0.05	<0.05*, NS†,‡
Triglycerides (mg/dl)	222.58±47.6	138.66±43.26	238.61±46.9	<0.0001	NS† <0.0001*,‡
HDL cholesterol mg/dl)	48.11±9.53	51.16±9.72	41.35±7.3	>0.05	NS* <0.01†,‡

P<0.05 were considered statistically significant. NS: Nonsignificant, *NMP versus PrMP, †NMP versus SMP, ‡PrMP versus SMP. PrMP: Premenopause, NMP: Natural menopause, SMP: Surgical menopause, BMI: Body mass index, BP: Blood Pressure, LDL: Low-density lipoprotein, HDL: High-density lipoprotein Intergroup comparison was done using one-way ANOVA followed by *post hoc* multiple comparison test

Table 2: Multiple comparisons and descriptive analysis of arterial properties of the study participants

Dependent variable	NMP ($n=64$)	PrMP ($n=32$)	SMP ($n=31$)	*P*	Intergroup comparison (*P*)
AoSys BP, mmHg	123.44±20.7	107.4±8.5	117.7±16.2	0.001	NS† <0.01*,‡
AoDia BP, mmHg	80.4±10.3	73.2±7.9	80.2±7.9	0.01	NS† <0.05*,‡
AoPP, mmHg	37.5±14.1	42.5±11.6	44±13.9	0.002	NS†,‡ <0.001*
AoAugP, mmHg	10.9±7.9	4.5±2.7	7.3±5.8	0.001	NS‡ <0.05*,†
cfPWV (cm/s)	1061.03±362.23	867.04±170.8	1104.4±234.6	0.002	NS† <0.005*,‡
baPWV (cm/s)	1573.2±544.6	1262.4±221.3	1775.8±604.12	0.002	NS† <0.005*,‡
ABI	1.14±0.093	1.12±0.05	1.13±0.23	0.818	NS‡,*,†

*NMP versus PrMP, †NMP versus SMP, ‡PrMP versus SMP. NS: Nonsignificant, NoPrMP: Premenopause, NMP: Natural menopause, SMP: Surgical menopause, AoSys BP: Central aortic systolic blood pressure, AoDia BP: Central aortic diastolic blood pressure, AoPP: Central aortic pulse pressure, AoAugP: Central aortic augmentation pressure, cfPWV: Carotid femoral pulse wave velocity, baPWV: Brachial ankle pulse wave velocity, ABI: Ankle brachial index

The physiological basis of these relations has not been fully revealed, although recent data from the WHI observational study attribute the increased CVD risk with hysterectomy to an adverse cardiovascular risk profile.[8] It is likely that menopause is associated with an increase in inflammation, which in turn results in increased stiffening of the vasculature and increased risk of cardiovascular outcomes.[9] However, our results demonstrating that women with surgical menopause have a greater arterial stiffness (reduced arterial compliance) compared to women with natural menopause and premenopausal, provides evidence for a possible physiological effect of hysterectomy on arterial health. In contrast to previous observational studies,[2,8,9] we only included women who were normotensive, nonsmokers, nondiabetic and not taking cardiovascular or lipid-lowering medications, thus removing some potential influence of overt disease and medication status on the vascular wall. Finally, surgical menopause status remained a significant predictor of large and medium-sized arterial stiffness and compliance after considering for surgical menopause risk factors (BMI and central aortic blood pressure) that were associated with indices of arterial stiffness (cfPWV, baPWV). In the current study, our data signifies that the greater arterial stiffness observed in women with surgical menopause explains independently the physiological effect of hysterectomy on the arterial wall. Since arterial stiffness is considered a biomarker of vascular aging, is an independent predictor of CVD and the root cause of morbidity and mortality.[12] The study results suggest that the increased CVD risk with surgical and natural menopause may be mediated through acceleration in vascular aging. The mechanisms by which menopause increases arterial stiffness in women are not clear. In women, increase in arterial stiffness appears to be increased after menopause, most probably due to estrogen deficiency.[13] As such, surgical menopause and the consequential estrogen deficiency may be a prospective mechanism for the obvious acceleration in large and medium artery stiffness with hysterectomy. Estrogen has been revealed to influence factors that contribute to arterial stiffness including the structural composition within the arterial wall (increased elastin and decreased collagen) and the contractile properties of vascular smooth muscle cells leading to increased nitric oxide bioavailability.[16-19] In the present study, we found that the influence of hysterectomy on arterial stiffness was similar to other observational studies of increased cardiovascular risk in women with hysterectomy.[2,8] However in the current study women with surgical menopause had an arterial stiffness (cfPWV, baPWV) more than women with natural menopause that is consistent with other study which states that mortality rates may be increased in women with early menopause, either spontaneous or surgically induced.[20]

CARDIA study[21] observed that neither hysterectomy nor NM appeared to influence subsequent changes in CVD risk factors after adjustment for antecedent risk factors. Their results were consistent with results from SWAN among women in midlife, hysterectomy regardless of ovarian status is not a major determinant of CVD risk factor status.[22] The CARDIA and SWAN suggest that premenopausal levels of CVD risk factors are predictive of levels of postmenopausal CVD risk factors. However, they also advocate that hysterectomy might influence short-term changes in some CVD risk factors.

Surgical menopause has been attributed to early and premature ovarian failure related to interference in ovarian blood flow with hysterectomy.[2] Cardiovascular risk is a public health concern in women after menopause,[23] and the results of the present study provide new insight into the possible pathophysiological role of hysterectomy on CVD risk in healthy women. In particular, our observations demonstrate that healthy women with hysterectomy have accelerated vascular aging compared to women with natural menopause and premenopausal independent of cardiovascular risk factors. Vascular aging is a major risk factor for the development of CVD, and accelerated vascular aging may manifest into early CVD events.[24] Hormonal dysregulation may contribute to the initiation and progression of CVD.[25-27] There is significantly deranged lipid profile (LDL-C, TC, and TG) in NMP and SMP group compare to PrMP group even after a wide variation in an age in NMP and SMP. This shows that estrogen withdrawal has a greater impact on CVD risk represented by deranged lipid profile compared to age. Some other studies revealed that deranged lipids are widely thought to be influenced by the menopausal transition[28] or menopausal status.[29] A better physiological understanding is needed to explain the effects of surgical menopause or premature menopause and the onset of estrogen

deficiency on the mechanisms initiating vascular aging leading to alteration in arterial properties.

A likely limitation of the present study could be the small sample sizes in the surgical menopause group compared to the natural menopause group. We trusted on participants' statement of the duration of menopause, duration following hysterectomy, and thus, it may be possible that this information and the classification of groups may not be totally accurate. We also cannot rule out other inherent factors that can influence arterial stiffness in women with surgical or natural menopause. In addition, we included healthy nonsmoking, normotensive, sedentary postmenopausal women without evidence of chronic diseases in our study; hence, our findings can only be extrapolated to this population of women.

Conclusions

The study results reveal that women with surgical menopause are associated with greater arterial stiffness when compared to women with natural menopause and premenopause. Large and medium-size arterial stiffness may be an important mechanism by which hysterectomy increases the risk of CVD in postmenopausal women.

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Conflicts of interest

There are no conflicts of interest.

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