Does Arterial Stiffness Increase in Patients with Surgical Early Menopause?

Cerrahi Erken Menopoz Geçiren Hastalarda Damar Sertliği Artar mı?

Murat AKÇAY [1] , Metin ÇOKSEVİM [1] , Ömer GEDİKLİ [1] , Hasan ULUBAŞOĞLU [2] , Özcan YILMAZ [1]

[1] Department of Cardiology, Faculty of Medicine, Ondokuz Mayis University, Samsun,TURKEY
[2] Clinic of Obstetrics and Gynecology, Samsun Education and Research Hospital, University of Health Sciences, Samsun, TURKEY

Abstract

Background: Surgical early menopause is early menopause due to medical reasons rather than the natural aging process. Pulse wave velocity (PWV) and augmentation index (AIx) are simple and non-invasive parameters for assessment of arterial stiffness. The aim of this study investigated the arterial stiffness in the surgical early menopause patients.

Materials and Methods: We included 40 patients with surgical early menopause and 40 healthy controls for the study. The patients' arterial stiffness and hemodynamic parameters were measured with Mobil-O-Graph NG (IEM GmbH, Stolberg, Germany) 24-hour ambulatory blood pressure monitor arteriography.

Results: There was no difference between the groups in baseline demographic, laboratory, and echocardiographic parameters except ejection fraction, glucose, and ALT values. In patients with surgical early menopause (n=40), the etiology was malignancy in 27 (67.5%), myoma in 11 (27.5%) and bleeding in 2 (5%) patients. PWV was significantly higher in the early menopause group (6.5 m/s, (4.7-8.2) versus 5.6 m/s, (4.5-9.0 m/s); P<0.001), but there was no statistically significant difference in AIx (28.3±10.9% versus 27.4±9.0%; P=0.69). Also, there was no statistically significant difference in terms of cardiac hemodynamic parameters and central aortic pressures.

Conclusions: Arterial stiffness is significantly increased in surgical early menopause patients compared with healthy subjects independent of other risk factors.

Key Words: Arterial stiffness, Pulse-wave velocity (PWV), Surgical early menopause

Öz.

Amaç: Cerrahi erken menopoz, doğal yaşlanma sürecinden ziyade tıbbi nedenlerle meydana gelen erken menopozdur. Nabız dalga hızı (NDH) ve büyütme indeksi (Augmentasyon indeksi, AIx), arteryel sertliğin değerlendirilmesi için basit ve invazif olmayan parametrelerdir. Bu çalışmanın amacı, cerrahi erken menopoz hastalarında arteryel sertliği araştırmaktır.

Materyal ve Metod: Çalışmaya cerrahi erken menopozlu 40 hasta ve 40 sağlıklı kontrol dahil edildi. Hastaların arter sertliği ve hemodinamik parametreleri, Mobil-O-Graph NG (IEM GmbH, Stolberg, Almanya) 24 saatlik ambulatuvar kan basıncı monitör arteriyografisi ile ölçüldü.

Bulgular: Başlangıç demografik, laboratuvar ve ekokardiyografik parametrelerde ejeksiyon fraksiyonu, glukoz ve ALT değeri dışında gruplar arasında fark yoktu. Cerrahi erken menopozlu hastalarda (n=40) etiyoloji değerlendirildiğinde 27 hastada (% 67.5) malignite, 11 hastada (%27.5) miyom ve 2 hastada (%5) kanama idi. Nabız dalga hızı (NDH), erken menopoz grubunda (6.5 m/s, (4,7-8,2) 5.6 m/s'ye (4,5-9,0 m/s) karşı anlamlı olarak daha yüksekti; P<0,001), ancak AIx'te istatistiksel olarak anlamlı bir fark yoktu (%28.3±10.9'a karşı %27.4±9.0; P=0.69). Ayrıca kardiyak hemodinamik parametreler ve santral aort basınçları açısından istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: Cerrahi erken menopoz hastalarında arteryel sertlik, diğer risk faktörlerinden bağımsız olarak sağlıklı bireylerle karşılaştırıldığında önemli ölçüde artmıştır.

Anahtar kelimeler: Arteryel sertlik, Nabız dalga hızı, Cerrahi erken menopoz

Introduction

Menopause is a physiological condition in women and a part of the natural aging course (1). The incidence of cardiovascular disease (CVD) is lower in premenopausal women, but it cumulatively increases after the menopause, especially after surgical menopause (2). A lot of evidence strongly supports the role of estrogen in reducing a woman's risk of developing cardiovascular disease (1). The cardiovascular changes often occur asymptomatic during the menopausal transition; however, symptom and frequency of atherosclerotic diseases increase postmenopausal period (2). On the contrary, there is no premenopausal transition period in women undergoing surgical menopause. The surgical removal of the ovaries results in the discontinuation of sudden hormone production, which has adverse effects on many organs and system, particularly the cardiovascular system (1,2).

Arterial stiffness is a marker of endothelial dysfunction. It develops from dynamic and complex interactions in the changes of cellular and structural elements in the vessel wall. The previous studies have demonstrated that arterial stiffness is a marker and prognostic factor for hypertension, chronic renal failure, stroke, dementia, heart failure, acute coronary syndromes, and especially atherosclerotic diseases (3,4). The pulse wave velocity (PWV) and augmentation index (AIx) are easily measurable, non-invasive parameters and used to evaluate arterial stiffness. PWV is also considered as gold standard method for measuring arterial stiffness (3-5).

In this study, we aimed to investigate arterial stiffness using Mobil-O-Graph NG (IEM GmbH, Stolberg, Germany) 24-hour ambulatory blood pressure monitor arteriography in the surgical early menopausal patients.

Materials and Methods

Study protocol

The present study was planned cross-sectional and observational study. We included 40 patients with surgical early menopause and 40 healthy controls for the study. Patients who entered surgical menopause for various reasons in the medical faculty of obstetrics and gynecology clinic, were scanned retrospectively from the automation system and the patients were called to the outpatient clinic. The control group consisted of female patients of similar age who applied to the obstetrics and gynecology outpatient clinic with different complaints. All patients' age, body weight, height, cardiovascular risk factors, current medications and other systemic diseases were recorded. Also, the surgical early menopause duration and cause were recorded. The exclusion criteria were accepted as surgical menopause duration less than a year, ongoing estrogen replacement therapy, history of chemotherapeutic drug using, improper measurement of blood pressure, history of coronary artery disease, heart failure and cardiomyopathy.

All patients were informed about the study and gave written consent. The protocol was accepted by the ethics committee of Faculty of Medicine, Ondokuz Mayis University (No: 2017/455) and adhered to the Declaration of Helsinki.

Measurement of arterial stiffness

Mobil-O-Graph NG (IEM GmbH, Stolberg, Germany) 24-hour ambulatory blood pressure monitor arteriography was used to measurement of arterial stiffness and cardiovascular hemodynamic parameters. The measurements were taken from brachial artery with a suitable size cuff in the sitting position. The measurements were performed in a silent, heat-controlled room (22 - 24°C), in the early morning time and avoided from eating, or drinking alcohol, coffee or tea for at least before 12 hours. The device inflated the cuff automatically up to at least 35 mmHg above the measured pressure value until no blood flow through the brachial artery. The blood flow was cut off as a result of occlusion by the brachial artery during the measurement period of a maximum of 20 sec. At the point where blood flow was cut off, a membrane was formed in the brachial artery at the upper edge of the inflated cuff. The waves generated by the central pressure changes described above were detected and augmented by the cuff with sensitive pressure sensors at this membrane level and then transferred to the device's dedicated tonometer. The waves recorded by tonometry and evaluated after uploading to HMS Client Server 5.1® software. The measurement validation of this device about the arterial stiffness and hemodynamic parameters was demonstrated with invasive and non-invasive methods in the previous studies (6-8).

The systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), pulse pressure (PP), central systolic blood pressure (cSBP), central diastolic blood pressure (cDBP), peripheral vascular resistance (PVR), pulse wave velocity (PWV), augmentation index (AIx), and cardiac output (CO) parameters were recorded with this device (Fig. 1).

Echocardiography

The echocardiographic evaluation was performed in the left lateral decubitus position from standard acoustics views with Vivid 7 device (GE Medical System, Horten, Norway; 3.5-MHz phased array transducer). The left ventricle end-diastolic and end-systolic dimensions, interventricular septum, and posterior wall thickness were measured in parasternal long-axis view. Ejection fraction was calculated by modified Simpson method. M-mode, two dimensional (2-D), Doppler and colored Doppler echocardiographic parameters of all patients were obtained and evaluated according to American Society of Echocardiography standards.
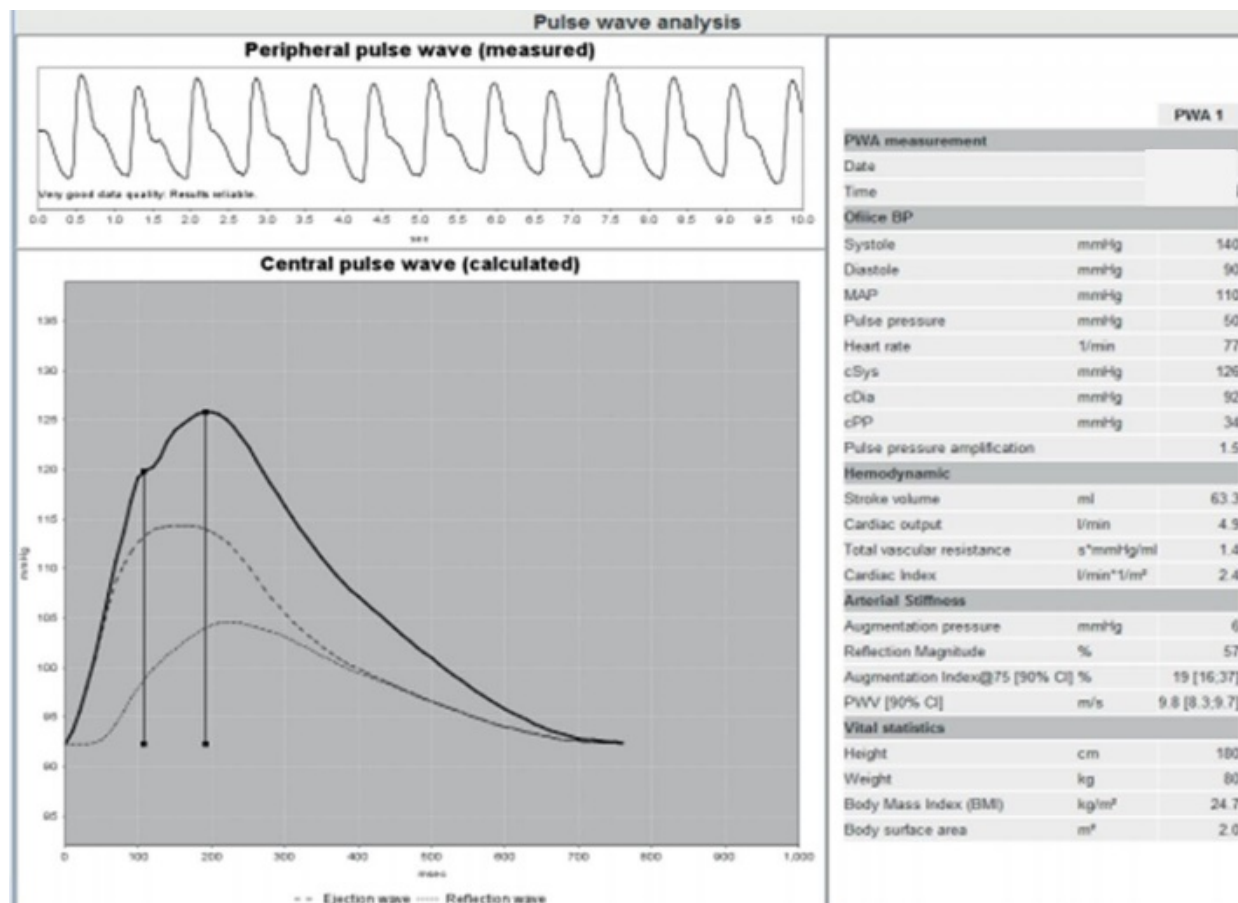
Figure 1. Basic parameters in the pulse wave record analysis with Mobil-O-Graph NG (IEM GmbH, Stolberg, Germany) 24-hour ambulatory blood pressure monitor arteriography.

Statistical analysis

The research data was uploaded to a computer and evaluated via "SPSS (Statistical Package for Social Sciences) for Windows 20.0 (SPSS Inc, Chicago, IL)". The Shapiro-Wilk test was used to determine the normality of distribution of continuous variables. Categorical variables were represented as numbers and percentages, continuous variables were represented as the mean ± SD when normal distribution was present and as median (minimum-maximum) if the variables revealed non-normal distribution. Pearson's Chi-square test and Fisher's exact test were used to assess categorical variables. To determine of statistically significant differences between two independent groups, if the variables unsuitable for normal distribution, Mann-Whitney's U-test was used; if the variables suitable, Student's t-test was used. A *P* value of < 0.05 was accepted as statistically significant.

Results

The study included 40 surgical early menopause patients and 40 control subjects with similar clinical demographic characteristics. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) operation in the surgical early menopause patients were performed due to malignancy or a mass suspicious to be malignant (n = 27, 67.5%), myoma (n = 11, 27.5%) and bleeding (n = 2, 5%). The surgical early menopause duration was median 20 month (minimum 14 month, maximum 48 month). There were no statistically significant differences (P > 0.05) between the surgical early menopause and control groups, in terms of age and body mass index (BMI), smoking status, the presence of hypertension, and diabetes mellitus. The baseline descriptive characteristics were presented in Table 1.

Ejection fraction values were significantly lower in the early menopause group (P = 0.008). Other echocardiographic and baseline laboratory parameters were found similar in both groups (P > 0.05). The glucose and alanine transaminase (ALT) values were significantly higher in the surgical early menopause group (P = 0.012 and P = 0.013, respectively) (Table 2). The heart rate and cardiac output were significantly high in the early menopause group compared to the control group (P = 0.008; 0.040, respectively) (Table 3). On the other hand, there were no statistically significant differences in terms of systolic, diastolic, mean blood pressure, pulse pressure, central systolic and diastolic blood pressure, and peripheral vascular resistance (P > 0.05). Pulse wave velocity (PWV) was significantly higher

in the surgical early menopause group compared to control group (6.5 m/s, (4.7-8.2 m/s) versus 5.6 m/s, (4.5-9.0 m/s); P < 0.001), but there were no significant differences

in terms of augmentation index (28.3 ±10.9% versus 27.4 ±9.0%; P = 0.69) (Table 2).

Table 1. Distribution of baseline clinical, laboratory and basic echocardiographic parameters between surgical early menopause and control groups

Variable	Surgical early menopause group (n = 40) Mean ± SD Median (IQR) *	Control group (n = 40) Mean ± SD Median (IQR) *	P value
Age (year)	43.7±5.6	41.8±6.1	0.167
BMI (kg/m²)	29.5 (20.1-38.2) *	28.1 (22.1-37.9) *	0.096
Cigarette, n (%)	7 (18.4)	11 (28.9)	0.280
Hypertension, n (%)	8 (21.1)	5 (13.2)	0.361
Diabetes mellitus, n (%)	2 (5)	1 (2.5)	0.980
Drugs, n (%)			
Beta-blocker	4 (10)	5 (12.5)	0.943
Metformin	2 (5)	1 (2.5)	0.980
Acetil salicylic acid	4 (10)	3 (7.5)	0.940
SSRI	7 (17.5)	5 (12.5)	0.865
Ejection Fraction (%)	60.1 (60-62)	61.1 (60-68)	0.008
LVEDD (mm)	42.9±4.5	41.1±4.0	0.067
LVESD (mm)	28.4±4.6	27.0±3.1	0.262
IVS (mm)	10.0 (8-12) *	9.4 (7-12) *	0.090
PW (mm)	9.6±1.4	9.4±1.4	0.585

BMI: Body mass index, IVS: Interventricular septum, IQR: Interquartile range, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, SD: Standard deviation, SSRI: Selective serotonin re-uptake inhibitor, PW: Posterior wall.
The (*) sign shows median and interquartile range values.

Table 2. Distribution of baseline laboratory parameters between surgical early menopause and control groups

Variable	Surgical early menopause group (n = 40) Mean ± SD Median (IQR) *	Control group (n = 40) Mean ± SD Median (IQR) *	P value
Glucose (mg/dl)	94.7 (74-134) *	88.5 (75-156) *	0.012
Creatinine (mg/dl)	0.65±0.11	0.66±0.10	0.771
Hemoglobin (gr/dl)	12.0±1.2	12.5±1.2	0.079
White blood cell (10³/ml)	7.4 (5.4-10.8) *	6.8 (4.8-10.7) *	0.237
Platelete (10³/ml)	271.2±73.6	260.1±51.7	0.491
AST (U/L)	18.6 (14-38) *	16.4 (12-25) *	0.095
ALT (U/L)	16.4 (9-32) *	13.8 (9-40) *	0.013
Total cholesterol (mg/dl)	191.9±38.5	174.0±35.4	0.154
LDL (mg/dl)	120.2 (78.1-180) *	97.3 (50-190) *	0.070
HDL (mg/dl)	58.5 (35.2-100) *	56.2 (45-76) *	0.135
Triglyceride (mg/dl)	163.4 (55.8-300) *	101.9 (50-180) *	0.086

The (*) sign shows median and interquartile range values.
IQR: Interquartile range

Discussion

In the present study, arterial stiffness parameters were increased in the surgical early menopause patients compared to the healthy controls. To our knowledge, there was no previous research evaluating the influence of surgical early menopause on arterial stiffness and cardiac hemodynamic parameters.

While women are better protected against atherosclerosis during the productive period, yet this effect may change after menopause (2, 9). The speed of progression of atherosclerosis increases with menopausal transition and asymptomatic cardiovascular changes often occur in the post-menopausal period (9,10). In the post-menopausal period, deficiency of estrogen and progesterone hormones cause significant changes in lipid and carbohydrate metabolism, thus the atherosclerotic process accelerates, and cardiovascular diseases increase (9-11). This brings about the idea that these effects can be eliminated by hormone replacement therapy and ovarian protective surgical

treatment methods may be prevented cardiovascular diseases by maintaining the physiological balance in the body. However, hormone replacement therapy is contraindicated especially hormone sensitive malignant diseases, or it can be considered based on risk to benefit ratio (11). In our study, 67.5% of patients were operated due to malignancy or a suspicious malignant mass and also other patients did not receive hormone replacement therapy for different reasons.

After natural menopause, the ovaries maintain to produce androgens and other different hormones (12). These androgens are aromatized to estrogens in the adipose tissue. On the other hand, after surgical menopause, the hormone production or peripheral estrogen conversion does not occur due to removal of ovaries (12). For this reason, more changes and high cardiovascular effects are antici-

pated after the surgical menopause according to the physiological menopause (12,13).

Surgical menopause is appeared to have more effects on the lipid metabolism than physiological menopause and also seen to have higher CAD risk according to the physiological menopause (12, 14). However, in a study, the total and LDL cholesterol levels were found to be non-significantly higher after surgical menopause according to the natural menopause (12). In the present study, total cholesterol, LDL cholesterol, and triglyceride levels were found higher in the surgical menopause group, although not statistically significant. But the elevated fasting glucose and AST levels were found statistically significant. The effects of menopause on insulin resistance and carbohydrate metabolism were found consistent with high glucose levels in the present study. However, the deficiency of insulin and HgA1c levels are among the limitations of this study. A meta-analysis demonstrated that surgical early menopause caused the cardiovascular diseases and associated with significantly increased cardiovascular mortality, whereas natural menopause was not had such effects (15,16). The Nurse's Health Study found that women, who underwent bilateral oophorectomy without hormone replacement therapy, have a relatively increased risk of lethal myocardial infarction while those with hormone replacement therapy did not have this increased risk (17). Moreover, the data about the effects of hormone replacement on the cardiovascular system in postmenopausal period are also conflicting. Some prior observational studies showed a preventive effect (18). Conversely, some randomized trials even showed increased cardiovascular risk in women with hormone replacement therapy during the postmenopausal period (19,20).

Table 3. Distribution of arterial stiffness and central hemodynamic parameters between surgical early menopause and control groups

Variable	Surgical early menopause group (n = 40) Mean ± SD Median (IQR) *	Control group (n = 40) Mean ± SD Median (IQR) *	P value
Systolic BP (mmHg)	123.4 (95-160) *	119.5 (105-165) *	0.107
Diastolic BP (mmHg)	78.3±11.0	77.7±10.2	0.779
Heart Rate (beat/min)	81.0 (70-115) *	73.0 (60-100) *	**0.008**
Mean BP (mmHg)	99.7±12.4	96.1±9.6	0.158
Pulse Pressure (PP)	45.0 (30-68) *	41.7 (32-58) *	0.165
cSystolic BP (mmHg)	114.3±15.0	110.4±10.2	0.140
cDiastolic BP (mmHg)	80.0±11.0	77.4±8.5	0.260
Peripheral vascular resistance (PVR) (sec*mmHg/ml)	1.26 (0.7-1.4) *	1.28 (1.0-1.4) *	0.966
Cardiac output (CO) (L/min)	4.87 (3.5-6.6) *	4.66 (3.9-5.5) *	**0.040**
Augmentation index (AIx) (%)	28.3±10.9	27.4±9.0	0.698
Pulse wave velocity (PWV) (m/s)	6.5 (4.8-8.0) *	5.6 (4.6-8.7) *	**<0.001**

BP: Blood Pressure, c: Central. IQR: Interquartile range.
The (*) sign shows median and interquartile range values.

Non-invasive assessment of arterial stiffness, a marker of endothelial dysfunction, is used for cardiovascular risk assessment and early diagnosis of vascular injury (3, 21). The PWV has been suggested as the gold standard method for the evaluation of arterial stiffness. The AIx is also related to increased aging and blood pressure (3, 21). The increase in PWV shows arterial stiffening as a consequence of organic and functional changes in the vessel circulation (10). In a study that PWV was increased in postmenopausal women and was associated with death due to coronary artery disease and stroke in the following 10 - 12 years (22). In another study showed that the PWV was increased in the early postmenopausal period and suggested that this increasing was related to estrogen deficiency and postmenopausal increased cardiovascular diseases (23). The mechanical changes in the vascular wall due to estrogen deficiency may take longer than the deterioration of endothelial function (10). The menopause accelerates the age related increased arterial stiffness (24). However, it is not well known how premenopausal ovariectomy influences the PWV value. There was no important variation observed in the PWV values surgical early menopausal group in some studies. In a study, although a decline in the flow-mediated vasodilatation was noticed one week after ovariectomy, there were no important changes in the arterial

stiffness one year after ovariectomy (25,26). In our study, although the PWV was significantly higher in surgical early menopause patients, there was no statistically significant difference in terms of
Although most of the literature data reported an increased risk of women after surgical early menopause, some other data refused these results. In the observational study of the Women's Health Initiative, researchers reported that baseline CAD risk factors were worse in patients who had previously hysterectomy/oophorectomy; and which were the responsible for subsequent CVD conditions, these were the risk factors, not the oophorectomy (17,26,27). The obvious objections to the results of these studies were higher ratio of myocardial infarction (MI), stroke, deep vein thrombosis and congestive heart failure at the baseline of their study (but not before the hysterectomy/oophorectomy); on the other hand, the waist circumference, BMI, blood pressure and cholesterol levels were high before the hysterectomy or oophorectomy. These results

showed the negative CVD impact of the hysterectomy/oophorectomy performed years ago. A negative effect of prior hysterectomy/oophorectomy was already present at the baseline and this negative effect continued throughout the study (17,26). In the present study, the PWV was found significantly high in the surgical early menopause group compared to the control group, although there were no important variations in terms of risk factors. There is an increasing number of evidence that the deficiency of ovarian function before the time of physiological menopause is associated with a series of adverse outcomes. Surgical early menopause is associated with an increasing risk of menopausal symptoms, sexual dysfunction, early death, CVD, dementia, Parkinsonism, bone loss and osteoporosis. When planned the bilateral oophorectomy, these possible adverse results should be cautiously evaluated towards the possible advantages (2,13,17,26).

In our study, arterial stiffness and cardiovascular hemodynamic parameters were evaluated with oscillometric measurement method (Mobil-O-Graph NG (IEM GmbH, Stolberg, Germany) 24-hour ambulatory blood pressure monitor arteriography). The validation of the device and this method has been shown in the many previous studies (6-8). It is accepted as non-invasive, rapid, easy, cheap and the best reproducible method for assessment of large arterial stiffness (6-8). Considering the findings of this study, this method may help in defining the future cardiovascular risks in the surgical early menopause patients.

Study Limitations

The major limitation of this study that the estradiol level could not be measured. The cross-sectional design of our study was unable to evaluate the longitudinal relations and differentiate causality among arterial stiffness and surgical early menopause. In addition, some patients in the surgical early menopause group had previously received short-term hormone replacement therapy, but there was no history of drug use for the last one year. The operator dependent echocardiographic evaluation is another limitation of the study. The number of patients is limited in the study and therefore the results must be supported with large, randomized trials.

Conclusion

Arterial stiffness was observed to be significantly increased in surgical early menopause patients compared with healthy subjects independent of other risk factors. The long-term clinical significance of this effect and its relationship with atherosclerotic diseases should be investigated with prospective studies.

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