Arch Iran Med. December 2017;20(12):734-739

www.aimjournal.ir

ARCHIVES OF IRANIAN MEDICINE

Original Article

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Adverse Cardiometabolic Effect in Bilateral/Unilateral Oophorectomy Versus Natural Menopause: Results of Over a Decade Follow-up Among Iranian Women

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Abstract

Background: To compare metabolic changes in 3 groups of postmenopausal women: those who had undergone bilateral salpingo-oophorectomy + hysterectomy (BSO + H), those with hysterectomy ± unilateral salpingo-oophorectomy (H ± USO), and those who reached natural menopause during follow-up.

Methods: This longitudinal study was performed on 543 female participants of the Tehran Lipid and Glucose Study (TLGS) who experienced surgical menopause (BSO + H or H ± USO) or natural menopause over a 12-year period. During the follow-up period, changes in metabolic and biochemical profiles were compared between surgically and naturally menopausal women (NMW). In all groups, data was collected using questionnaires twice, at baseline and again after 3 years.

Results: Considering the women with natural menopause as the reference group, the odds ratio of metabolic syndrome was 5.0 in the surgically menopause due to BSO + H. Mean fasting blood glucose was also significantly higher in the H ± USO group, compared to the naturally menopausal, after adjustment for confounding variables.

Conclusion: The incidence of metabolic syndrome in the BSO + H group and that of fasting blood glucose in the H ± USO group were higher than NMW.

Keywords: Blood pressure, Diabetes, Serum lipoprotein, Waist circumference

Cite this article as: Farahmand M, Ramezani Tehrani F, Bahri Khomami M, Azizi F. Adverse cardiometabolic effect in bilateral/unilateral oophorectomy versus natural menopause: results of over a decade follow-up among Iranian women. Arch Iran Med. 2017;20(12):734–739.

Received: October 3, 2016, Accepted: October 18, 2017, ePublished: December 1, 2017

Introduction

Based on recent findings from the Women's Health Initiative, practitioners need to reconsider their treatment options to avoid increasing the risk of cardiovascular disease (CVD) in postmenopausal women.[1] Data shows that the number of postmenopausal years is associated with a rise in CVD risk, fasting insulin and glucose levels, and visceral adiposity.[2,3] Since the ovaries are complex endocrine organs (producing different hormones like androgens and estrogens), they are involved in various metabolic processes such as bone and lipid metabolism.[4]

Studies on the relationship between metabolic syndrome (MetS) and menopause have yielded different findings; some report relationships between menopause and risk factors of MetS[5] while another claimed that estrogen deficiency caused MetS (abdominal adiposity, insulin resistance, and dyslipidemia) in a female population women.[2] Hidalgo et al, however, showed that factors such as age, lifestyle and age at menopause were related with the risk of CVD and MetS in postmenopausal women.[6]

Hysterectomy is the second most common surgery performed in women. Results of the study by Matthews et al in 2013 showed that hysterectomy status with or without oophorectomy did not increase the risk of CVD.[7] In bilateral salpingo-oophorectomy (BSO), loss of endogenous estrogen may accelerate atherosclerosis development, consequently increasing the CVD risk.[8] Results of studies imply uncertainty about the effect of BSO on risk of CVD.[3] In the Mayo Clinic Cohort study on survival patterns after oophorectomy, mortality increased among women aged <45 years who underwent BSO, contrary to the findings of another study population.[9]

In this study, we compared CVD risk factors between surgical menopause such as bilateral salpingo-oophorectomy + hysterectomy (BSO+H) and hysterectomy ± unilateral salpingo-oophorectomy (H ± USO) with natural menopause status.

Materials and Methods

Samples

Of 5191 women, aged 20–60 years, 543 women (408 naturally menopausal women [NMW] and 135 surgically

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menopausal women [27 BSO+H and 108 H±USO]) met our eligibility criteria. This longitudinal study was conducted on a group of female participants from the Tehran Lipid and Glucose Study (TLGS). TLGS is an ongoing prospective study, initiated in 1998, with the aim of assessing the prevalence of non-communicable disease risk factors. Detailed information about TLGS has been published earlier.[10] Details of the selection of the study subjects are presented in Figure 1. Subjects selected for the purpose of this study were non-menopausal women, without MetS at initiation of the TLGS; they became menopausal during follow-up due to (1) BSO+H surgery, (2) H±USO surgery, or (3) the natural process of menopause.

In all groups, information an anthropometrics, demographics, lifestyle variables, various risk factors for non-communicable diseases and medical and reproductive histories, were collected at baseline and again after 3 years by trained interviewers during face-to-face interviews. Details on measurement methods have been published elsewhere.[11]

Definitions

Menopause was defined according to the World Health Organization (WHO): absence of menstruation for over 12 consecutive months.

Surgical menopause was defined as the absence of menstrual bleeding due to hysterectomy with or without oophorectomy and bilateral oophorectomy with or without hysterectomy.

MetS was defined, according to the joint interim Statement, as the presence of any 3 of the following 5 risk factors: (1) Abdominal obesity as waist circumference (WC) ≥ 95 cm for women according to population- and country-specific cutoffs for Iranians; (2) fasting blood sugar (FBS) ≥ 100 mg/dL or drug treatment; (3) Fasting triglycerides ≥ 150 mg/dL or drug treatment; (4) Fasting high density lipoprotein cholesterol (HDL-C) < 50 mg/

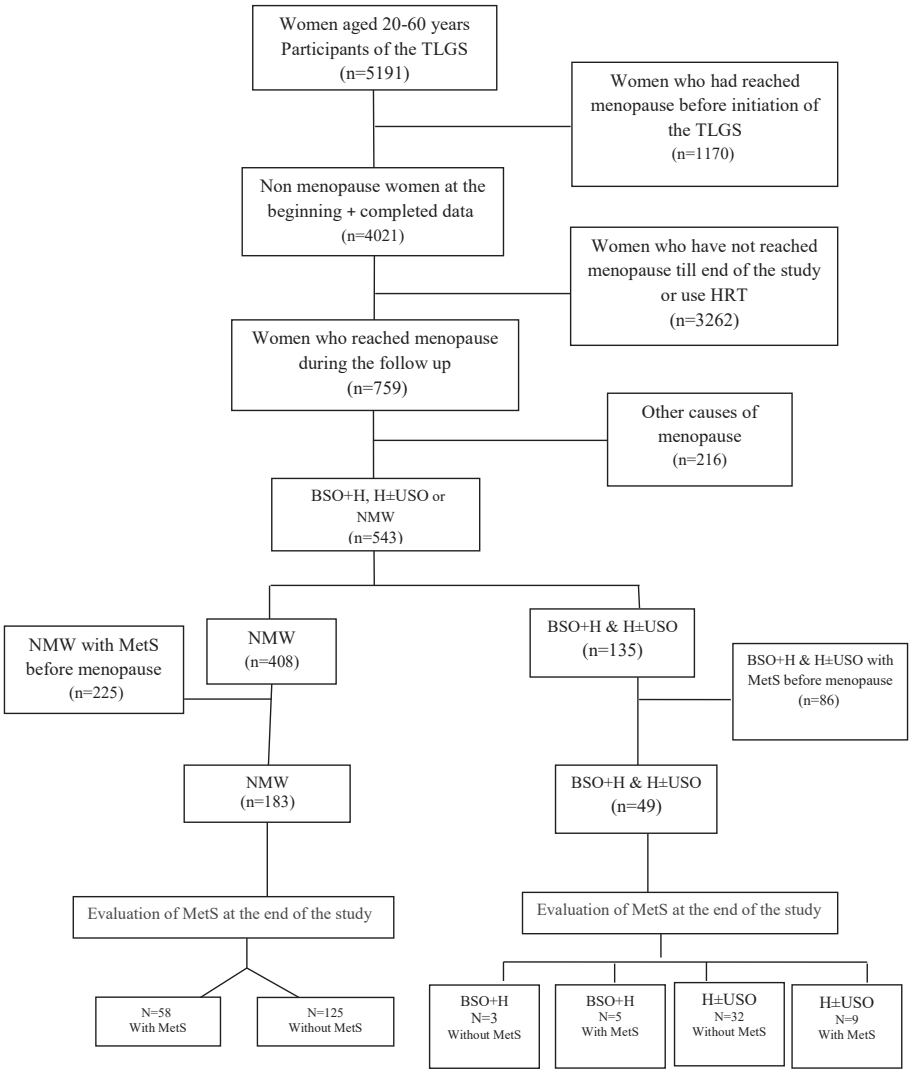

Figure 1. The Process of Sampling.
NMW, naturally menopausal women; MetS: metabolic syndrome; HRT, hormone replacement therapy; BSO+H: bilateral salpingo-oophorectomy + hysterectomy; USO±H, unilateral salpingo-oophorectomy ± hysterectomy.

Table 1. Demographic and Reproductive Characteristics and Biochemical Profiles of Naturally and Surgically Menopausal Women at Baseline

Variables	Natural Menopause	Surgical Menopause[a]	Surgical Menopause[b]
Demographics characteristics			
Age (y)	55.0 ± 4.3	49.8 ± 4.7	48.4 ± 3.9
BMI (kg/m^2)	28.6 ± 4.2	27.2 ± 3.2	28.5 ± 1.9
WC	89.1 ± 10.1	87.0 ± 9.7	88.7 ± 4.4
Reproductive history			
Birth (no.)	3.3 ± 1.5	2.8 ± 0.9	3.2 ± 0.7
Live births (no.)	2.0 ± 0.7	2.0 ± 0.0	2.0 ± 0.0
Biochemical blood factors			
TC (mg/dL), mean ± SD	205.3 ± 35.2	186.1 ± 35.1	215.9 ± 43.4
HDL-C (mg/dL), mean ± SD	46.7 ± 11.3	41.9 ± 9.5	35.3 ± 4.8
LDL-C (mg/dL), mean ± SD	130.5 ± 27.6	114.8 ± 27.1	136.5 ± 22.9
SBP (mm Hg), mean ± SD	115.2 ± 16.3	109.4 ± 12.7	115.8 ± 9.2
DBP (mm Hg), mean ± SD	75.6 ± 9.3	71.9 ± 8.4	77.1 ± 6.1
FBS (mg/dL), mean ± SD	89.8 ± 13.4	90.4 ± 15.0	88.3 ± 5.1
2hPG (mg/dL), mean ± SD	109.7 ± 32.3	104.0 ± 28.3	140.9 ± 48.3
TG (mg/dL), mean ± SD	143.9 ± 61.8	122.2 ± 52.3	245.6 ± 107.5
Smoking status, No. (%)	4 (2.2)	0 (0)	0 (0)
History of hyperlipidemia, No. (%)	31 (16.9)	7 (17)	0 (0)
History of hypertension, No. (%)	15 (8.2)	0 (0)	0 (0)
History of hyperglycemia, No. (%)	8 (4.4)	2 (4.9)	0 (0)

[a] Hysterectomy with or without unilateral oophorectomy (H±USO); [b] Bilateral oophorectomy with hysterectomy (BSO+H).
Abbreviations: BMI, body mass index; WC, waist Circumference; TC, total; cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; GTT, glucose tolerance test; TG, triglycerides; 2hPG: 2-hour plasma glucose.

Table 2. Association Between Menopausal Type and Biochemical Profiles

Variables	Model 1				Model 2			
	Coefficients[a–b] (95% CI for $\hat{\beta}$)	*P* Value	Coefficients[a–c] (95% CI for $\hat{\beta}$)	*P* Value	Coefficients[a–b] (95% CI for $\hat{\beta}$)	*P* Value	Coefficients[a–c] (95% CI for $\hat{\beta}$)	*P* Value
TC (mg/dL)	1.9 (-10.7–14.6)	0.8	-11.2 (-34.6–12.2)	0.3	1.7 (-11.9–15.2)	0.8	-4.6 (-30.4–21.1)	0.7
HDL-C (mg/dL)	2.5 (-1.8–6.8)	0.2	1.2 (-6.7–9.1)	0.8	0.9 (-3.7–5.6)	0.7	1.1 (-7.8–9.9)	0.8
LDL-C (mg/dL)	-1.1(-12.5–10.3)	0.8	-12.5 (-32.7–7.8)	0.2	-0.1(-12.0–11.8)	1.0	-8.3 (-30.2–13.6)	0.4
SBP (mg)	0.8 (-4.8–6.4)	0.8	2.4 (-8.0–12.7)	0.6	0.4 (-5.9–6.7)	0.9	0.8 (-11.2–12.8)	0.9
DBP (mg)	1.2 (-2.6–5.0)	0.5	2.5 (-4.5–9.5)	0.5	1.5 (-2.7–5.7)	0.5	3.5 (-4.4–11.4)	0.4
FBS (mg/dL)	6.3 (1.6–11.0) [d]	0.009	1.2 (-7.5–9.9)	0.8	6.3 (0.9–11.6)[d]	0.02	0.7 (-9.4–10.8)	0.9
2hPG (mg/dL)	7.0 (-7.1–21.1)	0.3	-14.4 (-40.1–11.2)	0.3	9.7 (-6.0–25.4)	0.2	-4.4 (-33.8–25.0)	0.8
TG (mg/dL)	3.2 (-21.8–28.2)	0.8	-0.5 (-47.5–47.4)	1.0	3.1 (-23.9–30.1)	0.8	9.8 (-43.2–62.8)	0.7

[a] *P* value of differences between baseline and final values in comparison to reference group (natural menopause); Model 1: Adjusted for age &WC; Model 2: Adjusted for model 1 & smoking status, history of hyperlipidemia, hypertension or hyperglycemia and medication for hyperlipidemia, hypertension or hyperglycemia; [b] Hysterectomy with or without unilateral oophorectomy (H±USO); [c] Bilateral oophorectomy with hysterectomy (BSO+H); [d] Statistically significant in comparison to reference group (natural menopause) ($P < 0.05$).
Abbreviations: TC, total; cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; TG, triglycerides; 2hPG: 2-hour plasma glucose.

dL in women or drug treatment and (5) Raised blood pressure defined as systolic blood pressure (SBP) ≥ 130 mm Hg, diastolic blood pressure (DBP) ≥ 85 mm Hg or antihypertensive drug treatment.

Laboratory Tests

Serum lipids and lipoproteins were measured after 124 hours of fasting, (7 PM to 9 AM); samples were centrifuged after 30 to 45 minutes following blood collection. All blood samples were analyzed at the TLGS research laboratory on the day of blood collection, details of which have been published elsewhere.[12]

Data Analysis

Baseline characteristics of women who had undergone natural menopause were compared to those who had undergone surgical menopause (the BSO + H or the H ± USO groups), using the analysis of variance (ANOVA) test for continuous variables and chi-square test for categorical variables.

Analysis of covariance (ANCOVA) was used to compare the differences between baseline and final values of continuous metabolic parameters between the study groups using 2 adjusted models: (1) Adjusted for age and WC and (2) Adjusted for age, WC and smoking status, history of hyperlipidemia, hypertension and hyperglycemia and medication for hyperlipidemia, hypertension or hyperglycemia.

Logistic regression was used to assess the risk of menopausal types on MetS after adjustment for age as a potential confounder.

It should be noted that we included women who were on treatment for lowering of lipids or blood pressure, as described in the criteria for definition of Mets. These subjects were, however, excluded in the analyses when we used the quantitative amounts of FBS, blood pressure (BP) and lipids. Data were analyzed using SPSS 15 (SPSS Inc., Chicago, IL, USA). *P* values ≤ 0.05 were considered statistically significant.

This study was approved by the ethical committee of the Research Institute for Endocrine Sciences (RIES), and written informed consent was obtained from all study participants.

Results

Table 1 shows the comparison of baseline demographics, biochemical and reproductive histories of the study subjects, according to their type of menopause; the baseline status was an average of 3 years before menopause in the study.

The ANCOVA test after adjustment for confounders in both models showed that mean FBS was significantly higher in the H±USO group compared to NMW (Table 2).

Incidence of MetS was 31.7%, 22% and 62.5% in the NMW, H±USO and BSO+H groups, respectively. Odds of MetS in the BSO +H group was 5.0 times higher than the NMW after adjustment for age using logistic regression (odds ratio: 5.0; CI: 1.1–24.1; $P = 0.04$).

Discussion

Findings of this study showed that the odds of MetS was 5.0 times higher in women with BSO+H, compared with their NMW counterparts.

The etiology of MetS is unclear; however, it is considered a multi-factorial disorder. Estrogen deficiency in postmenopausal women has been noted as an etiology for emergence of several metabolic or cardiovascular risk factors in this population.[2] It has been confirmed that the pathophysiology of the MetS is associated with increased visceral obesity and insulin resistance.[13] The CVD risk attributed to MetS appears to be particularly elevated in women, and it is estimated that about 50% of all cardiovascular outcomes in women are associated with MetS.[14] Although MetS may not be a single disease, it is a group of closely associated risk factors that jointly suggest a significant increase in CVD risk.[15] Postmenopausal status is associated with a 60% increased risk of the MetS, even after adjusting for confounding variables, such as age and body mass index (BMI).[16]

Our findings showed that serum lipid profiles in both surgically menopause groups compared to NMW were not significantly different after adjustment for potential confounders.

The ovaries are complex endocrine organs which are involved in many metabolic processes such as lipid metabolism.[17] A study conducted on the effects of menopause on serum lipids showed that changes in TG and low density lipoprotein cholesterol (LDL-C) levels were both dependent on age and BMI and changes in total cholesterol (TC) level were age-dependent.[18]

The Framingham Study reported that serum cholesterol levels rose in the transition phase from pre- to postmenopausal status in BSO.[19] Results of a prospective study showed that natural menopause had no effect on TC levels.[20] Considering that various confounding variables have been adjusted in different studies, some variation in the results is justifiable.[8]

The present study showed significantly higher mean FBS in the H±USO group compared to NMW after adjustment for confounders in both models. Although the reason of the association between H±USO and diabetes is unclear, the findings of this study suggest a probable hormonal-metabolic mechanism to explain the enhanced risk of diabetes involving women with USO.

Postmenopausal status is related with an increase in FBS and fasting insulin levels.[2] However, the results of a number of studies comparing the impact of menopause and aging on diabetes showed this relationship to be unclarified.[21] Menopause is characterized by an increase in a number of chronic conditions, with diabetes being an important one.[22] The relationship between estrogen and diabetes in postmenopausal women is doubtful, despite one study reporting that estrogen therapy decreased the risk of diabetes in postmenopausal women.[23] The impact of BSO on the risk of diabetes has not been widely studied.[22] It has been shown that transition to menopause is associated with an increase in estradiol, but not androgens[22] whereas hysterectomy with ovarian preservation was reported to be a cause of minor reduction in testosterone levels but not estradiol levels. However, BSO causes a sudden marked decline in serum estradiol levels in premenopausal women and a reduction in testosterone levels.[24] It has been demonstrated that ovarian hormones control the function of pancreatic β-cells,[25] and also that estrogens enhance insulin-induced

glucose transport.[25] Data show that the shorter the exposure to endogenous estrogen, the higher the diabetes risk in women with a shorter reproductive life span.[21]

Appiah et al reported that menopausal women with BSO+H are associated with higher incidence of diabetes, without adjustment for confounding variables. Other factors such as BMI, WC and smoking status did not alter this association.[22]

The hysterectomy-related cardiovascular risk, especially accompanied by BSO, is also unclear.[7] One mechanism suggested for this BSO risk is that sudden cessation of endogenous estrogen may promote the development of atherosclerosis, the most important factor leading to higher rates of coronary heart disease.[8] In the Framingham Heart Study, women who underwent hysterectomy, especially hysterectomy + BSO, were later at increased risk for CVD, adjusting for age group and smoking status.[3] Results of the Nurse's Health Study showed that women who had a BSO, usually in the fifth decade, were at greater risk for incident coronary heart disease.[26] In one study, women who had had hysterectomy, despite ovarian preservation, had raised levels of CVD risk factors and were more often diabetic and hypertensive, compared to postmenopausal women without hysterectomy.[27] Considering that various confounding variables have been adjusted in different studies, some variation in the results is justifiable.[8] Hysterectomy might also impact short-time variations in some CVD risk factors. Findings from several studies show no evidence that USO or BSO are independent predictors of increased levels of postmenopausal risk factors after adjustment for potential confounders. In this regard, results of a longitudinal study showed no difference in CVD risk factors almost two years before and after natural or surgical menopause.[7,28] On the other hand, in our study, data was gathered almost 3 years before menopause as baseline and again at menopause. In other words, we did not have adequate data after several years of menopause in participants.

Regarding strengths and limitations, our study has the advantage of using an ongoing population-based cohort with an average follow-up of 12 years, which allowed us to investigate the effects of different types of menopause on cardiometabolic disturbances after adjustment for premenopausal metabolic characteristics. The long-term follow-up with precise anthropometric and serum measurements and their comparison with similar studies are other strengths of the present study. The amount of intra-assay variability in our data is likely to be minimal because all laboratory measurements were done simultaneously at the same laboratory by the same person.

The small sample size was our main limitation. In addition, developing a cardiovascular risk is relatively a chronic condition which needs decades of follow-up from birth to death, for which further studies with longer follow-up periods are needed.

In conclusion, the incidence of MetS in the BSO+H group was higher than in the naturally menopausal with adjustment for age.

Authors' Contribution

MF contributed to the study design, data analysis, manuscript drafting and critical discussion. FRT contributed to the study design and execution, data analysis, manuscript drafting and critical discussion. MBH contributed to the data analysis and manuscript drafting. FA contributed to the study design and execution and manuscript drafting.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

This study protocol has been approved by the Medical Ethics Committee of the Research institute for Endocrine Sciences (approval number: 32ECRIES409/2289).

Acknowledgments

We appreciate the substantial time and effort the study participants contributed to this study. Acknowledgements are also due to research staff at the Tehran Lipid and Glucose Study Unit and staff of the Research Endocrine Laboratory. The authors wish to acknowledge Mrs. Niloofar Shiva an academic member of the Research Institute for Endocrine Sciences and a native speaker of the language for critical editing of English grammar and syntax of the manuscript. We thank the National Council of Scientific Research of the Islamic Republic of Iran for approval of this project and for its funding as a national research project.

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