ORIGINAL ARTICLE

Age of Natural Menopause and Related Factors among the Tabari Cohort

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Objectives: The age of menopause is affected by several factors. In this study we aimed to identify the age of natural menopause and its related factors in a large-scale population-based cohort in Iran.

Methods: In this study, a subset of data collected during the enrollment phase of the Tabari cohort study was utilized. Reproductive history and other related data were collected using a structured questionnaire. Blood samples were obtained from all participants. Data were analyzed using chi-square test, independent t test, and ANOVA as well as a multivariate linear regression model.

Results: Among participants of the Tabari cohort, 2,753 were menopausal women. The mean age of natural and induced menopause was 49.2 ± 4.7 and 43.2 ± 6.4 years, respectively (P = 0.001). The number of pregnancies, duration of breastfeeding, level of education, residency, presence of thyroid disease, and body mass index affected the age of menopause. After adjustments for confounding variables, the number of pregnancies remained significantly associated with late menopause.

Conclusions: The age of natural menopause in this study was similar to that in other studies, and the number of pregnancies was positively associated with the age of menopause after adjustments for confounding variables.

Key Words: Menopause, Natural fertility, Pre-menopause, Tabari cohort study

INTRODUCTION

Loss of menstruation is a common occurrence for women and leads to suppression of ovarian function. Level of estrogen decreases and eventually combines with menstrual cessation [1]. Influence of menopause on functions of endocrine, cardiovascular, skeletal, immune, and genitourinary systems has been reported previously [2].

The age of menopause is affected by many factors including genetic factors, obesity, alcohol consumption, social levels, ethnicity, education, diet, vitamin D and calcium intake, menarche age, long-term menstrual cycles, oral contraceptive use, and exposure to pesticides [1-4]. The World Health Organization has stated that by the year 2030, globally, there will be more than 1.2 billion women suffering from menopause along with obesity and high body mass index (BMI) and moreover it has been reported that every year 47 million women enter this stage of their lives [1].

Premature or early menopausal symptoms related to the progressive reductions in hormonal secretion and ovarian estrogen deficiency [5], moreover risk of cardiovascular diseases and its related morbidity are higher in women with earlier age at menopause [6]. There are varieties of definitions regarding early menopause.

So if the last menstruation occurs between the age of 40 to 44 and before the mid age of 51, we could define it as premature or early ovarian function failure [7,8]. Symptoms of menopause include hot flashes, sweating, sleep disorders, mental changes, and menstrual disorders. Later in the menopause period, vaginal atrophic changes and related sexual dysfunctions, cardiovascular diseases, osteoporosis, psychosocial changes, and muscular-articular complaints may appear. These symptoms accompanied with amenorrhea and lack of estrogen hormone [5]. Early menopause increases the incidence of cardiovascular disease and osteoporosis, in the other word for each year of delayed menopause. Two percent of the mortality rate from cardiovascular disease is reduced [9].

The age of menopause significantly differs based on genetic background, ethnicity, region, and country. Moreover socio-economic level, environment, lifestyle, reproductive, or early childhood factors are related with menopausal age [10]. It has been reported that women in developing countries experience menopause earlier than women in developed ones [6,11,12]. In the present large-scale population based cohort study we aimed to identify the age of natural menopause and its related factors in women who lived in north of Iran.

MATERIALS AND METHODS

In the study, we utilized a subset of data which was collected for Tabari cohort study (TCS). TCS is part of the national cohort, Prospective Epidemiological Research Studies in Iran (PERSIAN) [13,14]. The objective and details of TCS have been explained elsewhere [15]. Enrollment phase of the study started in June 2015 and ended in November 2017. In total 10,255 individuals, aged 35–70 years, living in urban (7,012), and mountainous areas of Sari (3,243), Mazandaran, Iran, were enrolled in TCS.

Data collection method includes structural questionnaire and obtaining blood, urine, hair, and nail samples. The questionnaire used in the study was a standardized questionnaire in which details and features are described in cohort profiles [13,14]. Items of questionnaire consist of general information, socioeconomic status, occupational history, type of fuel used, characteristics of the habitat, life style, history of fertility, history of chronic diseases, drug use, familial history of diseases, oral health, physical examination, physical disabilities, sleep status, physical activity, personal habits (smoking and drinking), food frequency, food supplements, water drink, dietary habits, and exposure to pesticides. To explain the reproductive section of the questionnaire in more details, we asked women about the age at menarche, first pregnancy age, number of pregnancies and abortions, duration of breastfeeding, use of contraceptive, and age of menopause (if happens) kind of menopause (natural or induced menopause).

Blood pressure and anthropometric indices were measured for all participants. All anthropometric indices include height and weight and waist and hip circumferences were measured by trained nurses in accordance with PERSIAN protocol [16].

Data were analyzed using IBM SPSS Statistics 24.0 (IBM Corp., Armonk, NY, USA). Variables were described using percentage, minimum, maximum, mean, and standard deviation. Categorical and quantitative variables were compared in two groups using chi-square and independent t test respectively. ANOVA was used to compare quantitative variables in more than two groups.

In order to adjust possible confounding variables, we used the multivariate linear regression model. Variables with P value less than 0.2 were considered in model, which include number of pregnancy, breastfeeding duration, educational level, marital status, residency, thyroid diseases (women who self-reported to clinically diagnosed with thyroid disease or receiving thyroid related medicine), and BMI. Socio-economic status was categorized into five levels. Socio-economic status was calculated using principal component analysis. We considered different variables consist of tripe (inside and outside of country), reading book, and access to computer and internet, owning car/motorcycle, and some home appliances such as dishwasher, washing machine, freezer, and vacuum cleaner. All mentioned variables scored and based on total number socio-economic status was categorized into five levels as following level 1, poorest; level 2, poor; level 3, moderate; level 4, good; level 5, richest. It should be noted that the correlation coefficient between the number of pregnancies and the number of live births was equal to 0.918 and therefore only number of pregnancy entered the multivariate linear regression model.

TCS was approved by Mazandaran University of Medical Science ethical committee (IR.MAZUMS. REC.1395.2524). Written informed consent form was obtained from all participants.

RESULTS

Among all participants of TCS, 2,753 were menopause women. The mean age of menopause was 47.9 ± 5.7 years with a minimum of 23 and a maximum of 64 years. The prevalence of normal menopause was 77.7% (2,140), and the prevalence of induced menopauses (due to surgery) was 22.3% (613). The mean age of natural and induced menopause was 49.2 ± 4.7 and 43.2 ± 6.4, respectively ($P = 0.001$). In the present article we focused on natural menopause and its related factor, the following analysis, women who menopause naturally were included. Figure 1 shows the number of women who included in our analysis. The average age of the menarche, number of pregnancies, number of children, the age at the first pregnancy, number of abortions, length of breastfeeding, and the age at the first marriage of participants are summarized in Table 1.

The history of infertility and contraceptive use in women who experienced menopause was 6.4% (136 of 2,140) and 47.8% (1,023 of 2,140), respectively. We compared the mean age of menopause in different socio-economic levels (five levels with level 1 as the lowest level and level 5 as the highest socioeconomic level) using ANOVA test. The mean age of menopause at the lowest and highest socioeconomic level was 49.5 ± 5.2 and 49.1 ± 4.1, respectively ($P = 0.276$). The mean age of menopause in women with and without history of infertility did not differ significantly (49.2 ± 4.7 vs. 49.6 ± 4.8; $P = 0.382$). Moreover there was no significant difference between the mean age of menopause in women who used contraceptive and who did not (49.3 ± 4.7 vs. 49.2 ± 4.8; $P = 0.529$). We compared the mean age of menopause in women with different marital status (single, married, widow, and divorced) and our analysis did not reveal any significant differ-

ence (47.3 ± 5.1, 49.2 ± 4.7, 49.7 ± 5.4, and 49.3 ± 3.2, respectively; $P = 0.110$). On the other hand the average age of menopause differed significantly according to the educational level ($P < 0.001$). The mean age of menopause in women who lived in mountainous region was significantly higher than women who lived in urban area (49.8 ± 5.1 vs. 48.9 ± 4.5; $P = 0.001$).

The correlation coefficient between menopausal age with abortion, breastfeeding duration, age at the first pregnancy, number of pregnancies, age at the first marriage, and age of menarche was calculated and results are given in Table 1. With increasing the number of pregnancy and duration of breastfeeding, the age of menopause significantly increased ($P < 0.001$).

We compared the age of menopause in women with and without thyroid disease. Our results showed that the age of menopause in women with thyroid disease is significantly lower than women without thyroid diseases (48.8 ± 4.7 vs. 49.4 ± 4.8; $P = 0.023$). Moreover we compared the age of menopause in women with and without diabetes (49.5 ± 4.9 vs. 49.2 ± 4.7; $P = 0.226$) as well as women with and without hypertension (49.4 ± 5.0 vs. 49.2 ± 4.7; $P = 0.266$) and our result did not show any significant differences between these groups.

We compared the age of menopause based on BMI (women divided into three groups: less than 25, 25–30, and greater than 30). Our finding showed that with increasing BMI, the age of menopause decreased (Table 2).

After adjustment of possible confounding variables (number of pregnancy, breastfeeding duration, educational level, marital status, residency, thyroid diseases, and BMI), number of pregnancy was still related with menopausal age. Multivariable regression analysis showed that with each unit increase in number of pregnancy and breastfeeding duration, the age of menopause increased by 0.08 and 0.06, respectively (Table 3).
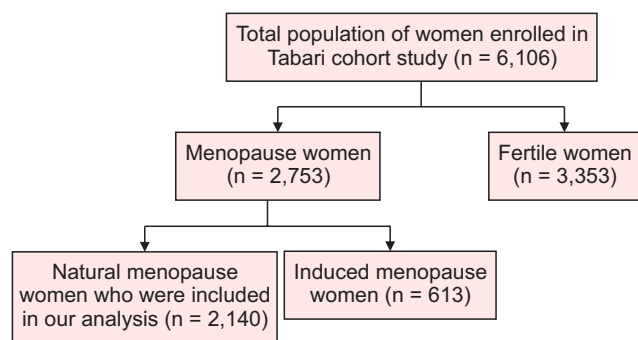

Fig. 1. Flow chart of women who were included in our analysis.

Table 1. Characteristic of study participants and its association with menopause age

Variable	Mean ± standard deviation	Correlation coefficient (*P* value)
Age of menarche (y)	13.8 ± 1.8	0.019 (0.391)
Number of pregnancy	5.1 ± 2.6	0.127 (< 0.001)
Number of live births	4.6 ± 2.2	0.159 (< 0.001)
Age of the first pregnancy (y)	20.8 ± 4.4	0.015 (0.490)
Number of abortion	0.5 ± 0.8	−0.022 (0.315)
Breastfeeding duration (mo)	83.9 ± 48.0	0.126 (< 0.001)
Age of the first marriage (y)	19.5 ± 4.9	−0.003 (0.889)

Table 2. Mean of natural menopausal age based on selected variables

Variable	Menopausal age	P value
Educational history		< 0.001
Illiterate	49.7 ± 5.1	
1–5 y	48.5 ± 4.6	
6–8 y	48.8 ± 4.5	
9–12 y	48.9 ± 4.1	
University	49.1 ± 4.2	
Marital status		0.110
Single	47.3 ± 5.1	
Marriage	49.2 ± 4.7	
Widow	49.7 ± 5.4	
Divorce	49.3 ± 3.2	
Soci-economic status		0.276
Level 1 (lowest)	49.5 ± 5.2	
Level 2	49.4 ± 4.9	
Level 3	49.1 ± 4.6	
Level 4	48.9 ± 4.6	
Level 5 (highest)	49.1 ± 4.1	
Residency		0.001
Urban	48.9 ± 4.5	
Rural	49.8 ± 5.1	
Thyroid disease		0.023
Yes	48.8 ± 4.7	
No	49.4 ± 4.8	
Diabetes		0.226
Yes	49.5 ± 4.9	
No	49.2 ± 4.7	
Hypertension		0.266
Yes	49.4 ± 5.0	
No	49.2 ± 4.7	
Body mass index (kg/m^2)		0.037
< 25	49.8 ± 5.1	
25–30	49.3 ± 4.8	
> 30	49.1 ± 4.7	
Smoking		0.249
Yes	47.4 ± 3.4	
No	49.3 ± 4.8	
Waist circumference (cm)		0.893
≥ 88	49.3 ± 4.8	
< 88	49.3 ± 4.9	
Waist to hip ratio		0.410
> 0.85	49.3 ± 4.8	
≤ 0.85	49.1 ± 4.9	

Data are presented as mean ± standard deviation.

Table 3. Association of natural menopausal age with selected variables using multivariate linear regression

Variable (reference)	Standardized beta coefficient	P value
Thyroid (no)	−0.03	0.194
Residence (urban)	0.04	0.113
Pregnancy number	0.07	0.025
Breast feeding duration	0.06	0.078
Educational level (illiterate)		
1–5 y	−0.03	0.138
6–8 y	0.01	0.682
9–12 y	0.02	0.483
University	0.03	0.305
Marriage (single)		
Married[a]		
Widow	0.03	0.173
Divorce	0.01	0.722
Body mass index (< 25 kg/m^2)		
25–30	−0.03	0.269
≥ 30	−0.04	0.233

[a]The number of single participants was very low (19 individuals vs. 1,802 individuals), so therefore we could not include it in the model.

DISCUSSION

Results of our study showed that the mean age of menopause in total population was 47.9 ± 5.7 and the mean age in natural and induced menopause was 49.2 ± 4.7 and 43.2 ± 6.4, respectively. Although the overall mean of menopause in our study is relatively similar to other province in Iran [11,12,17-19], the mean age of natural menopause in Tabari cohort population is greater than other provinces except Hamedan (49.6 ± 4.0) [20]. Comparing to other countries, age of menopause in our study is less than Western world [6,21], but it is higher than Punjabi women (47.9 ± 3.2) [22]. It has been reported that different factors such as environmental and genetic factors influence the age of menopause [23]. Result of our study showed educational level and residency affected the menopausal age although after adjusting for confounding variables neither of them remained significant. Natural menopause age indicates women health status as early menopause is associated with increased risk of cardiovascular disease and osteoporosis and late menopause is related with increased risk of breast and endometrial cancer

[21].

Our finding also showed that among reproductive variables, number of pregnancy was related to menopausal age. This relationship remained significant after adjustment for confounding variables. Moreover education, residency, thyroid disease, and BMI affected age of menopause. Results of Kaczmarek' study in Poland [21] showed that age at menarche, parity, and use of oral contraceptives was related to age at menopause. In this study we did not find any association between age at menarcheal and menopausal age. This association has not been reported consistently in previous studies.

Parity is often found to be positively associated with later age of menopause [21,24]. In this study there was a significant association between the numbers of pregnancy with age at menopause.

Association between marital status and menopausal age was inconsistent in previous studies [19,20]. In our study the number of single participants was very low and therefore we could not compare them with married participants.

Unlike the previous studies, results of present study did not show any significant relationship between socioeconomic level and menopausal age.

BMI is one of the factors related with menopausal age. In the present study women with lower BMI had significantly higher menopausal age but after adjustment of confounding variables there was no association between BMI and menopausal age. Association between BMI and age at menopause has been reported inconsistently. Some studies found no association between BMI and age of menopause [22], whereas others found higher BMI associated with later menopause [25-27].

We also compared age of menopause in women with and without some diseases. Among them history of thyroid disease was significantly related with menopausal age but diabetes and hypertension were not related with age at menopause. Multivariable regression analysis did not confirm association between thyroid disorder and age at menopause.

Cigarette smoking is the most established and consistently observed risk factor for younger age at menopause, with estimates of impact about one year with a clear dose-response association [28]. In the present study the number of smoker was very low, and therefore no association between smoking and menopausal age was observed.

Some limitation of the present study should be considered that first, reproductive history of women was self-reported of events years back in their life which can be subject to recall bias, and moreover remembering the exact time of menopause might be subject to recall bias as well. Second one, we did not include women older than 70 years old who may face more severe health related problems.

Results of the present study showed that the age at natural menopause was similar to other studies and number of pregnancy was positively associated with menopausal age after adjustment for confounding variables.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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