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Prevalence of Primary Ovarian Insufficiency, Early Menopause and their Associated Factors among Menopausal Women: Results from the AZAR Cohort study in Iran

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ABSTRACT

Background & aim: Primary ovarian insufficiency (POI) and early menopause are among the primary causes of female infertility. Thus, the present study evaluated the prevalence of POI and early menopause and identifies the associated factors in postmenopausal women in Shabestar, Iran.

Methods: This cross-sectional study was carried out useing data from the AZAR cohort study (ACS), which was conducted in Shabestar, Iran, from October 2014 to January 2017. Among 15,006 participants, fundamental data for 8,290 women were extracted, of whom 3,491 were in menopausal period. Data were collected using a structured and pre-designed questionnaire. To identify the prevalence of POI and associated factors, univariable and multivariable logistic regression were used.

Results: This study found that the prevalence of POI, early menopause, and age at natural menopause was 6.1%, 27.6%, and 66.3%, respectively. Multivariable logistic regression results, after adjusting for all potential confounding factors, revealed that the odds of POI were significantly lower in women with parity ≥ 3, overweight women, and women with late menarche. The odds of POI were also considerably higher in smokers. The results also revealed that underweight women had more than 4 times higher odds of early menopause.

Conclusion: The results revealed that parity, age at menarche, overweight, and smoking had a statistically significant relationship with POI. Due to the increasing prevalence of POI and early menopause, screening to identify the associated factors by healthcare providers will help to provide early interventions.

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Introduction

Menopause, as the end point of women's reproductive period, is considered a natural transitional process in women's lives (1). Permanent cessation of menstrual cycles for 12 consecutive months without any apparent psychological or pathological reason (such as bilateral oophorectomy, chemotherapy, or radiotherapy) is called natural menopause (2). The mean age of natural menopause is estimated to be 51.4 years, but it varies based on the geographical region (3).

Menopausal age is considered a very significant biomarker and indicator of ovarian function. Menopause before the age of 40 is classified as primary ovarian insufficiency (POI). Menopause between the ages of 40 and 45 is called early menopause (4). In the United States, about 5 percent of women experience menopause between the ages of 40 and 45 years. Also, 1% of women experience

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menopause before the age of 40 (5). The results of a meta-analysis study revealed that about a quarter of Iranian women experience menopause earlier than the age of 45 (6). The results of a survey from 9 cohort studies on 51,450 postmenopausal women reported the prevalence of POI and early menopause as 0.2% and 7.6%, respectively (7). The results of a systematic review study in Iran revealed that the prevalence of POI and early menopause is 3.7% and 12.2%, respectively (6).

Primary ovarian insufficiency is defined as the cessation of menstruation with a lack of serum estrogen and an increase in follicle-stimulating hormone (FSH) more than mIU/L40, at the age of less than 40 years, with approximately 2 standard deviations lower than the mean age of natural menopause (8). Therefore, POI occurs at least 10 years before the mean menopause age of 51.4 years (9). The manifestations of POI include one of the symptoms of secondary amenorrhea or oligomenorrhea, infertility, and estrogen deficiency. POI and early menopause can occur spontaneously and be induced (10).

The causes of POI are very heterogeneous. The guideline development group of the European Society of Human Reproduction and Embryology (ESHRE) has classified the causes of POI into 6 categories: chromosomal or genetic defects, iatrogenic causes, infections, autoimmune disorders, environmental factors, and idiopathic factors (11). The results of a study of more than 11,000 Australian women revealed that women with POI were almost three times more likely to develop multiple diseases in their sixties than women with natural menopause (12). In other words, women with POI experience the effects of estrogen deprivation for a longer period, which is associated with many complications.

POI and early menopause are associated with many psychosocial and physiological problems, including increased risk of osteoporosis (13), cardiovascular disease (14), type 2 diabetes (15), Alzheimer's (16), early death (17), depression (18), and low quality of life (19). Several factors are involved in determining the time of menopause and its deviation from the normal range. The results of a study by Vatankhah et al. (2023) on factors related to menopause showed that age, height, smoking, history of diabetes, hypertension, thyroid disease, depression, and use of hormonal contraceptives had a significant relationship with menopause (20).

The results of the Tehran lipid and glucose study (TLGS) using the Accelerated Failure Time (AFT) model showed that, compared with time of menopause in normal-weight women, it decreased by 0.09 and 0.03 years in underweight and overweight women, respectively. Also, the natural menopause time increased by 0.12 years in women who used oral contraceptives for more than 6 months (21). Since women in developing countries experience menopause earlier than women in developed countries (22), and since reported risk factors for early menopause, including female smoking, obesity, and early menarche, are increasing, it is crucial to determine the prevalence of POI and early menopause and identify the factors associated with it.

Although a significant relationship between POI and early menopause and the health status and quality of life of women has been reported, there is currently a dearth of knowledge about the prevalence of POI and early menopause and its associated factors, especially in the Asian population. Thus, identifying the aspects related to POI and early menopause, especially those that are modifiable, may be crucial for planning health and prevention interventions and improving the quality of life of postmenopausal women. Hence, this study evaluated the prevalence of POI and early menopause and identified the associated factors in postmenopausal women in Shabestar, Iran.

Materials and Methods

This cross-sectional study was conducted using data from the AZAR cohort study (ACS), as part of the prospective epidemiological research studies in Iran (PERSIAN cohort in Shabestar, one of the cities in East Azerbaijan province, Iran (23, 24). ACS is a population-based prospective cohort that aims to investigate non-communicable diseases (NCDs), including cardiovascular, gastrointestinal, liver, kidney, metabolic, respiratory disorders, and cancers. It was initiated in October 2014 and ended in January 2017. Details of this cohort study has been published elsewhere (25).

The inclusion criteria of the study included living in Shabestar city for at least 9 months and being aged 35 to 70 years. People with severe mental and physical diseases were excluded from the study. For sampling, almost all eligible people in small towns and villages were invited to participate in the study. Also, in bigger cities, more than 60% of the target population was asked (25). First, the list and medical records of all people aged 35 to 70 years were prepared by Shabestar Health Centers (East Azerbaijan Province, Iran).

After checking the inclusion and exclusion criteria, if the women were willing to participate in the study, written informed consent was obtained from them. Among 15006 participants, the basic data of 8290 women were extracted. In this step, women who never experienced menstruation in their lifetime (n=4) were excluded from the study. Finally, 8286 women entered the present study. Among them, 3491 were in menopausal period and provided reliable information about their menopause. According to the World Health Organization (WHO) classification, menopause is defined as the absence of spontaneous menstrual bleeding for more than 12 months without any other pathological or physiological cause (26). The time after the 12 months of no menstrual bleeding was considered the age of natural menopause (ANM). POI was defined as menopause before the age of 40, and early menopause was defined as menopause between the ages of 40 and 45 years (4).

Data were collected by trained interviewers using a valid and reliable questionnaire administered face-to-face (25). It included information related to socio-demographic and anthropometric characteristics such as age, age at menarche, BMI, gravidity, number of abortions, marital status, and educational level, quintiles of wealth index, smoking status, oral contraceptives, fertility drugs, infertility history, tubectomy, and hysterectomy history. To determine anthropometric indicators, BMI was calculated as weight (kg) divided by height (m) squared after measuring each participant's height and weight. BMI classification was used based on the World Health Organization. Accordingly, participants were classified into four different categories: (1) underweight (BMI < 18.5 kg/m2), (2) normal weight (BMI: 18.5-24.9 kg/m2), (3) overweight (BMI: 25.0-29.9 kg/m2, and (4) obese (BMI ≥ 30 kg/m2). Regarding smoking, smokers were those who continuously smoke at least one cigarette per day for more than half a year. Ex-smokers were people who used to smoke in the past but do not smoke now. Non-smokers had no history of smoking, and other tobacco users were those who smoked hookah and chewed snuff.

Socioeconomic status was estimated based on Wealth Score Index (WSI) using Multiple Correspondence Analysis (MCA) according to the variables such as access to a dishwasher, access to a computer, access to a car, price of a car, owning a mobile phone, number of international trips in a lifetime, and household amenities (e.g., number of rooms, ownership type). The participants of this study were divided into five classes based on WSI, ranging from poorest to richest. Fertility history information included age at menarche, gravidity, parity, number of abortions, use of oral contraceptive pills (OCP), history of taking fertility drugs, history of taking drugs for infertility, hysterectomy, and tubectomy.

To analyse data, SPSS statistical software (Version 25.0) (IBM Corp, Armonk, NY, USA) was used. Socio-demographic characteristics and the prevalence of POI and early menopause among participants were described using descriptive statistics, including frequency, percentage, mean, and standard deviation (SD). To estimate the prevalence of POI and early menopause, the probability of menopause events was used based on age. Women's menopausal age was classified into 3 groups with 5-year intervals based on available sources. Then, the menopause rate in each age group was estimated. Skewness and Kurtosis were used to determine the normality of the quantitative data. They indicated that the data followed a normal distribution. To determine the relationships between POI and early menopause and various variables, bivariate tests, including univariate logistic regression, were used to estimate crude odds ratios (cORs). Then, variables with p-values < 0.2 were entered into the multivariable logistic regression model to control for confounding. In the statistical analysis, the age at natural menopause was used

as the reference category. The results of multivariable logistic regression were presented as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). P-value <0.05 was considered statistically significant.

Results

In the present study, as part of the ACS study, 8286 participants were enrolled from Oct 2014 to Jan 2017. Among them, 3491 were menopausal. The mean age (SD) of the participants and their mean age of menopause (SD) in this study were 49.2 (9.3) and 47.4 (5.2), respectively. Almost over half of the women (60%) were over 45 years old. Regarding marital status, the majority of women (87.8%) were married. More than half of women (59.3%) menstruated for the first time in the normal age range (12-14 years). The majority of them (84.5%) were overweight or obese. More than two-thirds of the participants (71.5%) reported parity ≥3. The majority of them (94%) had less than a diploma. Also, more than two-thirds of them (73.8%) had a history of using oral contraceptive methods. Based on the WSI index, more than a quarter of women (27.5%) had a poor socioeconomic status. Also, the majority of women (92.3%) did not report a history of using drugs for infertility treatment. Table 1 presents other details related to demographic characteristics and anthropometric measures.

Table 1. Socio-demographic characteristics among studied women (N=8286)

Characteristic	N (%)
Age (Years)	
<40	1472 (17.8)
40-45	1841 (22.2)
>45	4973 (60.0)
Age at menarche (Years)	
Early<12	648 (7.8)
Normal (12-14)	4911 (59.31)
Late>14	2727 (32.9)
BMI (kg/m2)	
Underweight (<18.5)	(0.4) 33
Normal (18.5–24.9)	(15.1) 1249
Overweight/Obese (>25)	(84.5) 6996
Gravidity	
0	(5.4) 447
1-2	(23.1) 1918
≥3	(71.5) 5921
Number of abortions	
No abortion	(62.6) 4096
One	(24.4) 1912
≥2	(13.0) 1021
Marital status	
Single	(2.4) 199
Married	(87.8) 7271
Widow/divorced	(9.8) 816
Educational level	
Illiterate	(23.2) 1921
Primary school	(40.9) 3393
Intermediate/ High school	(29.9) 2477
University	(6.0) 495
Quintiles of wealth index	
1 (poorest)	(27.5) 2280
2	(17.8) 1474
3	(19.7) 1629
4	(20.6) 1703
5 (richest)	(14.5) 1200
Smoking status	
Never	(98.8) 8188
Ex-smoker	(0.5) 38
Smoker	(0.5) 39
Smoker of other tobacco products	(0.2) 21
Oral contraceptives	
Yes	(73.8) 6119
No	(26.2) 2167
Fertility drugs	
Yes	(5.6) 451
No	(94.4) 7636
Infertility history	
Yes	(7.7) 626
No	(92.3) 7461
Tubectomy	
Yes	(24.6) 2036
No	(75.4) 6250
Hysterectomy	
Yes	(4.2) 352
No	(95.8) 7934

BMI: body mass index

The prevalence of POI and early menopause

The results of this study revealed that the prevalence of POI (age less than 40 years), early menopause (age between 40 and 45), and menopause at natural age (age more than 45 years) was 6.1%, 27.6%, and 66.3%, respectively (Table 2).

Table 2. The prevalence of POI and early menopause (N=3491)

Menopause status	The prevalence of POI and early menopause, N (%)
POI (<40)	213 (6.1)
Early (40-45)	964 (27.6)
Natural (>45)	2314 (66.3)

POI: Primary ovarian insufficiency

Factors associated with POI and early menopause based on bivariate and multivariable analyses

Based on the univariate logistic regression test results, a statistically significant relationship was found between the variables of BMI (P=0.020), gravidity (P<0.001), parity (P<0.001), smoking (P<0.001), use of fertility drugs (P=0.036), history of infertility (P=0.005), and POI. Also, a statistically significant relationship was observed among BMI (P= 0.031), gravidity (P= 0.004), parity (P= 0.012), use of fertility drugs (P= 0.020), history of infertility (P= 0.041), and early menopause (Table 3).

Then, the variables that had P<0.2 were entered into the multivariable logistic regression model. After adjusting the demographic characteristics of the participants, the results of multivariable logistic regression showed that the odds of POI was significantly lower in women with parity≥3 (aOR 0.37; 95% CI 0.19 to 0.69, P=0.002), overweight women (aOR 0.61; 95% CI 0.39 to 0.96, P= 0.033), and women with late menarche (aOR 0.67; 95% CI 0.49 to 0.92, P= 0.014). In other words, women with parity≥3, overweight women, and women with a history of late menarche had lower odds of having POI by 63%, 39%, and 33%, respectively. Also, the odds of POI were significantly higher in smoking women (aOR 7.85; 95% CI 2.60 to 23.67, P<0.001). In other words, smoking increased the odds of POI almost 8 times (Table 4).

Table 3. Univariable logistic regression analysis for factors associated with POI and EM (N=1177)

Variable	POI (<40) (N=213)		EM (40-45) (N=964)	
	cOR (95% CI)**	P-Value	cOR (95% CI)**	P-Value
Age of menarche (Years)				
Normal (12-14) (Ref)	1		1	
Early <12	0.97 (0.58-1.63)	0.921	1.16 (0.88-1.544)	0.270
Late>14	0.74 (0.55-1.01)	0.060	1.07 (0.91-1.25)	0.380
BMI (kg/m2)				
Normal (18.5–24.9) (Ref)	1		1	
Underweight (<18.5)	2.84 (0.28-28.12)	0.370	4.67 (1.15-18.97)	0.031
Overweight (25-29.9)	0.60 (0.39-0.94)	0.020	0.95 (0.75-1.21)	0.708
Obese (≥30)	0.85 (0.57-1.27)	0.450	0.94 (0.74-1.19)	0.627
Gravidity				
<3 (Ref)	1		1	
≥3	0.53 (0.36-0.77)	<0.001	0.71 (0.57-0.89)	0.004
Parity				
<3 (Ref)	1		1	
≥3	0.49 (0.35-0.68)	<0.001	0.77 (0.63-0.94)	0.012
Number of abortions				
No abortion (Ref)	1		1	
One	1.02 (0.73-1.41)	0.886	0.94 (0.78-1.12)	0.511
≥2	0.74 (0.47-1.16)	0.196	0.97 (0.78-1.20)	0.780
Marital status				
Single (Ref)	1		1	
Married	1.64 (0.21-12.40)	0.628	0.73 (0.33-1.59)	0.430
Widow/divorced	1.73 (0.22-13.39)	0.595	0.81 (0.37-1.80)	0.619
Educational level				

Variable	POI (<40) (N=213)		EM (40-45) (N=964)	
	cOR (95% CI)**	P-Value	cOR (95% CI)**	P-Value
Illiterate	2.71 (0.65-11.26)	0.170	1.06 (0.65-1.73)	0.796
Primary school	2.98 (0.71-12.44)	0.133	1.06 (0.65-1.74)	0.801
Intermediate/ High school	2.42 (0.56-10.39)	0.232	0.82 (0.49-1.38)	0.471
University (Ref)	1		1	
Quintiles of wealth index				
1 (poorest)	1.378 (0.83-2.26)	0.207	1.24 (0.95-1.60)	0.102
2	0.98 (0.56-1.69)	0.947	1.05 (0.80-1.39)	0.683
3	1.26 (0.73-2.18)	0.397	1.02 (0.76-1.37)	0.861
4	1.0 (0.57-1.92)	0.866	0.91 (0.66-1.25)	0.563
5 (richest) (Ref)	1		1	
Smoking status				
Never (Ref)	1		1	
Ex-smoker	0.97 (0.22-4.14)	0.967	0.51 (0.19-1.37)	0.185
Smoker	8.67 (3.19-23.54)	<0.001	1.32 (0.44-3.96)	0.613
Oral contraceptives				
Yes	0.85 (0.63-1.14)	0.294	0.91 (0.77-1.07)	0.280
No (Ref)	1		1	
Fertility drugs				
Yes	1.86 (1.04-3.34)	0.036	1.51 (1.06-2.15)	00.02
No	1		1	
Infertility history				
Yes	1.93 (1.21-3.09)	0.005	1.35 (1.01-1.81)	0.041
Single	1.04 (0.13-8.11)	0.968	1.78 (0.71-4.46)	0.212
No (Ref)	1		1	
Tubectomy				
Yes	0.72 (0.50-1.02)	0.060	1.01 (0.85-1.20)	0.899
No (Ref)	1		1	
Hysterectomy				
Yes	7.06 (5.10-9.78)	<0.001	1.89 (1.47-2.43)	<0.001
No (Ref)	1		1	

POI: primary ovarian insufficiency, EM: early menopause, BMI: body mass index
*In this analysis, the age at natural menopause was considered as the reference category
**crude odds Ratio (95% Confidence Interval). The variables of age of menarche, BMI, gravidity, parity, and number of abortions, education, quintiles of wealth index, smoking status, fertility drug, infertility history, and tubectomy were identified
as independent variables associated with
the POI in the bivariate analysis with P < 0.2.
BMI, gravidity, parity, quintiles of wealth index, smoking status, fertility drug use, and infertility history were identified as independent variables associated with early menopause in the bivariate analysis (P < 0.2)

The results of multivariable logistic regression also showed that underweight women (BMI < 18.5) (aOR 4.12; 95% CI 1.0 to 16.9, P = 0.049) had more than 4 times the odds of early menopause.

Table 4. Multivariable logistic regression analysis for factors associated with POI and EM

Variable	POI (<40)		EM (40-45)	
	aOR (95% CI)**	P-Value	aOR (95% CI)**	P-Value
Age of menarche (Years)				
Normal (12-14)	1			
Early <12	0.99 (0.58-1.69)	0.996	-	-
Late>14	0.67 (0.49-0.92)	0.014	-	-

Variable	POI (<40)		EM (40-45)	
	aOR (95% CI)**	P-Value	aOR (95% CI)**	P-Value
BMI (kg/m2)				
Normal (18.5–24.9)	1		1	
Underweight (<18.5)	3.00 (0.29-31.05)	0.357	4.12 (1.00-16.91)	0.049
Overweight (25-29.9)	0.61 (0.39-0.96)	0.033	0.97 (0.76-1.24)	0.830
Obese (≥30)	0.85 (0.56-1.28)	0.440	0.97 (0.77-1.23)	0.790
Gravidity				
<3 (Ref)	1		1	
≥3	1.33(0.64-2.78)	0.436	0.80 (0.51-1.25)	0.333
Parity				
<3 (Ref)	1		1	
≥3	0.37 (0.19-0.69)	0.002	0.92 (0.62-1.37)	0.702
Number of abortions				
No abortion (Ref)	1			
One	1.03 (0.71-1.48)	0.862	-	-
≥2	0.71 (0.44-1.16)	0.178	-	-
Educational level				
Illiterate	4.28 (0.95-19.23)	0.058	-	-
Primary school	4.25 (0.96-18.74)	0.056	-	-
Intermediate/ High school	3.02 (0.68-13.31)	0.140	-	-
University (Ref)	1			
Quintiles of wealth index				
1 (poorest)	1.22 (0.70-2.12)	0.475	1.21 (0.93-1.57)	0.150
2	0.91 (0.50-1.65)	0.771	1.05 (0.79-1.39)	0.714
3	1.26 (0.70-2.25)	0.430	1.02 (0.76-1.37)	0.881
4	0.97 (0.52-1.83)	0.942	0.89 (0.64-1.23)	0.491
5 (richest) (Ref)	1		1	
Smoking status				
Never	**1**		1	
Ex-smoker	1.01 (0.23-4.44)	0.987	0.56 (0.21-1.49)	0.248
Smoker	7.85 (2.60-23.67)	<0.001	1.63 (0.53-5.02)	0.390
Fertility drugs				
No (Ref)	1		1	
Yes	0.78 (0.29-2.05)	0.619	1.22 (0.66-2.25)	0.550
Infertility history				
Single	0.55 (0.06-4.53)	0.579	1.32 (0.50-3.46)	0.631
Yes	1.42 (0.64-3.16)	0.382	1.02 (0.62-1.69)	0.905
No (Ref)	1		1	
Tubectomy				
No (Ref)	1			
Yes	0.73 (0.50-1.07)	0.110	-	-

POI: primary ovarian insufficiency, BMI: body mass index
*In this analysis, the age at natural menopause was considered as the reference category.
**Adjusted Odds Ratio (95% Confidence Interval)
***Significant (P < 0.05)

Discussion

The present study determined the prevalence of POI and early menopause and identified associated factors among postmenopausal women in the AZAR cohort study in Shabestar, Iran. The results revealed that the prevalence of POI, early menopause, and age of natural menopause is 6.1%, 27.6%, and 66.3%, respectively. Regarding the associated factors, the results indicated a statistically significant association between some socio-demographic and anthropometric characteristics and the occurrence of POI and EM.

The mean age of natural menopause in the present study was 47.4 years, consistent with

other studies conducted in the Iranian population (20, 22, 27). Generally, the mean age of natural menopause in the Middle Eastern population (46.9-47.8) is lower than in European (52.8-50.1) and American (50.5-51.4) countries (28). A reason for the difference between Iran and developed countries may be differences in lifestyle, public health, and the higher quality of health care in developed countries (29). In the present study, the prevalence of POI and early menopause was 6.1% and 27.6%, respectively. The overall prevalence of POI and early menopause varies between 1-5% and 5-10%, respectively, worldwide (30). The results of a systematic review and meta-analysis in Iran reported the prevalence of POI and early menopause at 3.7% and 12.2%, respectively (6).

Methodological differences may explain the differences in the results of the studies. In other words, the use of different approaches to estimate the prevalence of POI and early menopause in various studies can be considered the cause of this difference. Also, to evaluate the prevalence of POI, some studies determined it in the entire population, resulting in lower reported prevalence than the actual level (31, 32). The increasing prevalence of POI and early menopause in the Iranian population increases the significance of identifying the associated factors in the occurrence of these disorders.

The results of this study revealed that parity and age at menarche are associated with the occurrence of POI. In other words, the odds of POI in women with Parity≥3 and women with late menarche (age of menarche≥14) were 63% and 33% lower, respectively. In line with the results of our study, a study by Mishra et al. (2018) on 50,000 postmenopausal women from England, Scandinavia, Australia, and Japan showed that women who were nulliparous and had early menarche (age at menarche less than 12 years) compared to multiparous women (two or more children) and women with late menarche were at a greater risk of POI more than 5 times. In other words, early menarche alone increases the risk of POI by 80%, while this risk doubles for nulliparous women (7).

A possible explanation for the protective effect of parity against developing POI could be that ovulation stops during pregnancy. Hence, increasing parity results in more eggs in the ovaries, which helps prevent POI in women (33). Additionally, regarding the relationship between early menopause and POI, genetic studies have indicated that some menarche-related single-nucleotide polymorphisms (SNPs) predict natural menopause (34).

Overweight was another associated factor of POI in this study (BMI 25.0-29.9). Overweight women in the present study had 39% lower odds of developing POI. Obesity is associated with reproductive function and potentially with menopause time. However, the results of studies on the relationship between obesity and menopause are very contradictory. Some studies reported the odds of POI occurrence more in underweight women (35), and some reported its occurrence more in obese women (36). However, some studies have not reported any relationship (37). Consistent with the results of the present study, the results of a prospective cohort study by Szegda et al. (2017) on 78,759 postmenopausal women showed a non-linear relationship between BMI and menopausal age. Overweight women had 21-30% lower odds of developing POI compared to normal-weight women (38). Moreover, the results of another meta-analysis revealed a moderate relationship between overweight and menopause at a later age (39). In line with the results of the present study, the study by Rizvanović et al. (2022) showed that menopausal age increases with increasing BMI (40).

In contrast with the results of the present study, the study by Rostami Dovom et al. (2021) showed that the menopause time in underweight and overweight women is approximately 0.09 and 0.03 years, respectively, shorter than in normal-weight women (21). The difference in the results of the studies may be related to their cross-sectional design. Additionally, the protective effect of overweight on POI may be mediated by estrone production in adipose tissue in overweight and obese women, as adipose tissue is a vital site for the environmental production and metabolism of estrogen in women.

In adipose tissue, circulating androstenedione produced by the ovaries and adrenal glands is converted to estrone (a weak

form of estrogen) by the aromatase enzyme. The expression and activity of aromatase in adipose tissue increase as a function of body weight and age. Estrone contributes to a woman's total estrogen levels and is positively associated with body weight. It is believed that this excess estrogen contributes to delayed menopause (41). Another possible association between BMI and menopausal age is leptin production in adipose tissue. Leptin plays a role in transmitting information about the body's energy reserves to the hypothalamus and regulating normal reproductive function. A study found that early menopause is associated with low leptin levels (42). However, more studies are needed to confirm the relationship between leptin and menopausal age.

In contrast to the two mechanisms mentioned, another mechanism proposed for the relationship between BMI and POI is that anti-mullerian hormone (AMH) is produced by granulosa cells in the ovary. It is an indicator of ovarian reserve. Some studies have indicated lower levels of AMH among obese women compared to women of normal weight and reported that obesity is associated with an increased risk of POI (43). However, this claim has not been proven well since it is still unclear what leads to a reduction in AMH levels among obese women (44). In this regard, a study by Su et al. found that AMH levels do not differ between obese and normal-weight women (45).

Smoking was another factor associated with POI. The results of the present study revealed that female smokers are almost 8 times more exposed to POI. There are several hypotheses regarding the association between smoking and early menopause. The first hypothesis is that smoking may affect ovarian aging and follicle storage by affecting gonadotropins and sex steroids, and may also have toxic effects on ovarian germ cells (46). The second hypothesis is that smoking activates aromatic hydrocarbon receptors by producing polycyclic aromatic hydrocarbons (PAHs) (47).

In this regard, many studies reported an association between smoking and POI (48, 49). In line with the results of the present study, the results of pooled analyses of 17 observational studies conducted by Zhu et al. (2018) in seven countries, including Australia, Denmark, France, Japan, Sweden, England, and the United States, showed that current smokers are about 2 times more exposed to POI compared with never smokers. In other words, higher intensity, longer duration, higher cumulative dose, younger age at smoking initiation, and shorter time since smoking cessation were significantly associated with higher risk of POI (50). The results of the study by Vatankhah et al. (2023) in Iran also showed that women smokers had almost 2 times higher odds of POI (20).

Women's underweight (BMI < 18.5) was the only factor associated with early menopause identified in the present study. In other words, women with a BMI<18.5 were more than 4 times more likely to experience early menopause compared to normal-weight women. Consistent with the results of our study, the results of a study by Zhu et al. (2018) revealed that underweight women (BMI<18.5) compared to women with normal BMI (BMI=18.5-24.9) had more than twice the odds of early menopause, and overweight and obese women were almost 1.5 times more exposed to late menopause (2). The mechanisms related to underweight and early menopause are unclear, although some hypotheses have been proposed in this regard.

The proposed hypothesis is that women with a lower BMI (BMI < 18.5) have poor fat storage, which may lead to poor-quality ovarian follicles and, thus, POI (40). Also, low body weight increases the risk of functional hypothalamic amenorrhea (FHA), which leads to anovulation, hypoestrogenism, and an increased risk of infertility. Anovulation induced by disruption of the hypothalamic-pituitary-gonadal (HPG) axis is associated with early menopause (37).

To the best of our knowledge, this study is the first study conducted to determine the prevalence of POI and early menopause and the associated factors in postmenopausal women by classifying menopausal age into three different groups in Iran. The most significant strength of the study is the use of data from a cohort study of postmenopausal women, a large sample size, and the adjustment for potential confounding factors, including demographic and reproductivedata. Also, the comprehensive evaluation of women through a structured questionnaire covering many factors, such as

socio-demographic and anthropometric characteristics, and fertility history, is another strength of this study.

However, the present study suffers from some limitations. This study was cross-sectional and cannot investigate the causal relationships among variables and POI or early menopause. Also, regarding women's menopausal age, women's self-reported information about menopausal age was sufficient, which may have been subject to recall bias. Hence, to ensure menopausal age, future studies can perform hormonal tests to determine serum FSH and estradiol levels. We should treat with caution in interpreting the results obtained for smoking and underweight women due to the small sample size in these groups. The results of the study show that Iran's situation may differ from that of other countries due to differences in health system policies. Finally, more studies are needed to identify the associated factors of POI and early menopause by conducting longitudinal studies with larger sample size and following Iranian women from the early years of fertility to menopause.

Conclusion

The results of this study showed that the prevalence of POI, early menopause, and age of natural menopause is 6.1%, 27.6%, and 66.3%, respectively. Additionally, parity, age at menarche, overweight (BMI=25.0-29.9), and smoking had a statistically significant relationship with POI. Also, a significant statistical relationship was observed between underweight (BMI<18.5) and early menopause. Since women spend more than a third of their lives in menopause, and this period is associated with unpleasant side effects for many women, health policymakers should try to enhance women's knowledge about menopause, its symptoms, and ways to improve quality of life by integrating educational programs in health centers. In addition, due to the increasing prevalence of POI, early menopause, and their associated risk factors, screening to identify the related factors by healthcare providers in health centers will be helpful in preventing and providing early interventions to increase the quality of life of women and reduce the complications caused by these disorders.

Declerations

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Conflicts of interest

The authors declared no conflicts of interest.

Ethical considerations

Informed consent was obtained from all participants before data collection. Also, a comprehensive explanation of the study's goals and process, the confidentiality of information, and the freedom to withdraw from the study at each stage was provided to all participants before the start of the study. All ethical principles in the present study were observed in accordance with the Declaration of Helsinki.

Code of Ethics

The current study was approved by the Ethics Committee of Tabriz University of Medical Sciences (Ethical approval code: tbzmed.rec.1393.205).

Use of Artificial Intelligence (AI)

We have not used any AI tools or technologies to prepare this manuscript.

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Authors' contribution

MM and EF contributed to the study design. MM and SMA contributed to the implementation and analysis plan, and MM wrote the first draft of this article. All authors critically reviewed the text, contributed in revisions, and approved the final manuscript.

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