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Original Study

A prospective study on the relationship between polycystic ovary syndrome and age at natural menopause

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Abstract

Objective: This study aimed to determine whether polycystic ovary syndrome (PCOS) was associated with age at menopause, compared with women without PCOS, after adjusting for potential confounders.

Methods: A total of 1,696 reproductive-aged participants from the Tehran Lipid and Glucose Study were included in this population-based prospective study with a follow-up of approximately 20 years. Of these, 348 women with PCOS based on the Rotterdam criteria and 1,348 non-PCOS controls were followed to assess the age at which they reached menopause. An accelerated failure time survival regression model was used to identify the association between PCOS and the age at natural menopause (ANM), with and without adjustment for potential confounders.

Results: The unadjusted accelerated failure time survival model revealed a significant positive association between PCOS and ANM; PCOS women experienced time to menopause by a factor of 1.05 than non-PCOS controls (95% confidence interval, 1.02-1.06; $P < 0.001$). After adjusting for age at baseline, menarche age, history of hypertension, history of type 2 diabetes mellitus, parity, oral contraceptive use, body mass index, education level, physical activity, and smoking, the results remained significant (time ratio: 1.03; 95% confidence interval, 1.01-1.06; $P = 0.002$).

Conclusions: This study indicates that ANM is significantly associated with PCOS in women. Our study findings may have implications for the fertility and reproductive health of women with PCOS. However, further large longitudinal studies on diverse populations accounting for other relevant confounders are still needed to provide data on the actual difference in age at menopause and to elucidate the underlying mechanisms of this association.

Key Words: Age at natural menopause – Polycystic ovary syndrome – Tehran Lipid and Glucose Study.

The World Health Organization (WHO) defines menopause as the permanent cessation of menstruation due to the loss of ovarian follicle activity. Natural menopause is clinically defined as the permanent cessation of menstruation for at least 12 consecutive months after ruling out other pathological or physiological causes.[1] It is characterized by some hormonal alterations, such as reduced serum estrogen concentrations, a concomitant increase in follicle-stimulating hormone (FSH) levels, and undetectable values of anti-Müllerian hormone (AMH).[2-4] The timing of menopause onset is influenced by the initial size of the follicle pool and its depletion.[5,6] There is also evidence supporting the notion that women with polycystic ovary syndrome (PCOS) have a higher ovarian reserve, measured by antral follicle count (AFC) or AMH than normo-ovulatory women, which predisposes them to experience a later menstrual cessation.[7] The high ovarian reserve in PCOS patients suggests that these individuals may experience a delayed age at natural menopause (ANM) because of a slower rate of ovarian

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aging.[8,9] It has also been documented that gene variants related to age at menopause are associated with PCOS risk, possibly through the effects on FSH, luteinizing hormone levels, and follicle number; hence, women with PCOS may have a longer reproductive lifespan.[10,11]

Several studies have evaluated the ANM in women with PCOS; however, conflicting results have been reported.[8,12-19] In some studies, ANM was estimated in PCOS patients based on the serum level of AMH, as a biomarker of ovarian aging, which can predict the reproductive lifespan and age at menopause,[8,12-14,19] whereas other studies have assessed actual age at menopause in these patients.[15-18] The discrepancy between previous studies may be attributed to methodological issues, such as estimation of age at menopause based on the AMH level rather than the exact menopausal age, cross-sectional designs of studies, recall bias of retrospective research, nonpopulation-based design of studies, small sample size, and failure to adjust for substantial confounders.

With this background in mind, the present population-based prospective study, with a long-term follow-up, aimed to determine whether PCOS is associated with later age at menopause, compared with the non-PCOS controls, after adjusting for potential confounders.

METHODS

Study design and participants

Participants for our study were selected from among those who participated in the Tehran Lipid and Glucose Study (TLGS). The TLGS is an ongoing prospective cohort initiated in 1998, which assessed 15,005 participants 3 years or older.[20] In brief, information on various risk factors for noncommunicable diseases, demographic variables, and reproductive histories was collected during face-to-face interviews conducted every 3 years. To date, TLGS has completed even phases at 3-year intervals (phase 1, 1999-2001; phase 2, 2002-2005; phase 3, 2005-2008; phase 4, 2008-2011; phase 5, 2011-2014; phase 6, 2014-2017; and phase 7: 2017-2021). Current data are available for seven phases, including the baseline and six follow-up visits.

In the third phase of TLGS, we assessed the PCOS status of reproductive-aged participants (aged 20-45 y) using the Rotterdam criteria. Because PCOS is considered a lifelong diagnosis, the previous data collected in phases 1 and 2 are also considered (n = 2,941). We excluded those without any follow-up visit (n = 134), those with only hyperandrogenism (HA) (n = 433), those with only anovulation (AOV) (n = 233), and those with only polycystic ovary morphology (n = 167). Those

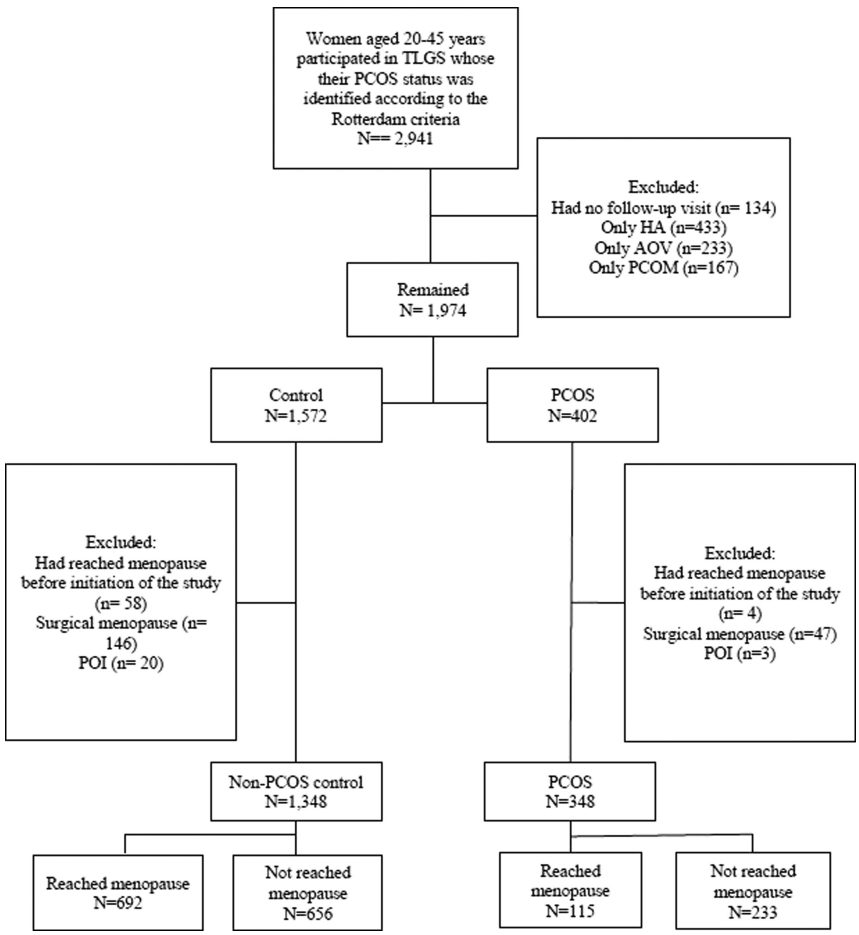

FIG. 1. Flowchart of the study. AOV, anovulation; HA, hyperandrogenism; PCOS, polycystic ovary syndrome; PCOM: polycystic ovary morphology; POI: premature ovarian insufficiency; TLGS, Tehran Lipid and Glucose Study.

women who were already menopausal (n = 62); those who had histories of hysterectomy, oophorectomy, or any other kind of surgery on their ovaries (n = 193); and those with premature ovarian insufficiency (n = 23) were also excluded. Among the remaining 1,696 participants, 348 women (20.5%) were diagnosed with PCOS, and 1,348 women (79.5%) were in the non-PCOS control group. All these women had at least one follow-up visit in addition to their two baseline and first follow-up visit.

During follow-up visits, 692 control women (51.3%) and 115 women with PCOS (33.0%) reached menopause, and their age at menopause was recorded; the remaining participants, including 656 women in the non-PCOS control group and 233 women in the PCOS group, who had not reached menopause were considered censored participants. Figure 1 illustrates the study flowchart.

Measurements

Medical, obstetric, and family histories were obtained from all study participants using pretested questionnaires.[21] Clinical and anthropometric measurements were assessed by trained examiners at each follow-up, as previously described.[22] In brief, weight was measured with participants minimally clothed using a digital scale (Seca 707, Seca GmbH) and rounded to the nearest 100 g. Height was measured without shoes in the standing position with shoulders in normal alignment, using a tape measure. Waist circumference was measured with an unstretched tape measure at the level of the umbilicus without any pressure on the body surface and recorded to the nearest 0.1 cm. Hip circumference was measured at the level of the anterior superior iliac spine without any pressure on the body surface. Body mass index (BMI) was calculated as weight in kilograms divided by height squared (square meters). Systolic blood pressure and diastolic blood pressure (DBP) were measured twice on the right arm with the participant in a seated position using a standard mercury sphygmomanometer after the participant had sat for 15 minutes; the mean of these two measurements was recorded.

Fasting plasma glucose was assayed using an enzymatic colorimetric method with glucose oxidase. Analyses were performed using related kits (Pars Azmon, Inc, Tehran, Iran) and a Selecta 2 autoanalyzer (Vital Scientific, Spankeren, the Netherlands). The intra-assay and interassay coefficients of variation for glucose were both 2.2%.

Dehydroepiandrosterone sulfate (DHEAS), 17-hydroxyprogesterone, total testosterone (TT), and androstenedione (A4) were measured by enzyme immunoassay using Diagnostic Biochem Canada Co (Ontario, Canada) kits. Sex hormone binding globulin (SHBG) was measured using immunoenzymometric assay with Mercodia kits (Uppsala, Sweden). All ELISA tests were performed using the Sunrise ELISA reader (Tecan Co, Salzburg, Austria). Prolactin and thyroid-stimulating hormone were measured by the immunoradiometric assay using Izotop kits (Budapest, Hungary) and a gamma counter (Wallac Wizard, Turku, Finland). The free androgen index (FAI) was calculated based on the following formula: TT (nmol/L) × 100/SHBG (nmol/L). Intra-assay and interassay coefficients of variation for TT were 3.6% and 6.0%; for DHEAS, 1.9% and 3.2%; for SHBG, 1.1% and 4.1%; for A4, 2.2% and 3.5%; for thyroid-stimulating hormone, 1.9% 3.4%; and for prolactin (PRL), 2.1% and 4.3%.

Term definition

According to the WHO classification, menopause was defined as the absence of spontaneous menstrual bleeding for more than 12 months, for which no other pathologic or physiologic cause could be determined.[1]

Polycystic ovary syndrome was diagnosed based on the Rotterdam criteria, which require the presence of two or more of the following: oligo/anovulation (ANOVU), hyperandrogenemia and/or HA, and polycystic ovaries.[23] Anovulation was defined as either regular or irregular menstrual cycles ≥34 days or those who had a history of eight or fewer menstrual cycles in a year. Hyperandrogenism was defined as hirsutism that was assessed based on a modified Ferriman-Gallwey scale with a cutoff value of ≥8, moderate acne, or androgenic alopecia.[24-26] Hyperandrogenemia was defined as an increased level of one or more serum androgens above the 95th percentile (0.89 ng/mL for TT, 2.9 ng/mL for A4, 179 mg/dL for DHEAS, and 5.39 for FAI).[27] Polycystic ovary was diagnosed by the presence of 12 or more follicles in each ovary, measuring 2 to 9 mm in diameter and/or increased ovarian volume of more than 10 mL.[28]

Hypertension was defined as mean systolic blood pressure of ≥140 mm Hg, mean DBP of ≥90 mm Hg, or current use of antihypertensive medicine. Systolic blood pressure ranges from 120 to 139 mm Hg and/or DBP of 80 to 89 mm Hg were defined as prehypertension.[29,30]

The American Diabetes Association criteria were used for diagnosing type 2 diabetes (T2DM) and pre-T2DM.[31] According to these criteria, T2DM was defined as fasting blood sugar (FBS) of ≥7 mmol/L, or 2-hour plasma glucose level of ≥11.1 mmol/L, or using antidiabetic drugs. Pre-T2DM was considered as impaired fasting glucose with FBS levels between 5.6 and 6.9 mmol/L or impaired glucose tolerance with 2-hour plasma glucose levels that were 7.77 to 11.1 mmol/L.

For evaluating physical activity, a modified activity questionnaire was used, which is evaluated and validated in the Iranian population. Physical activity has been specified as low (MET, <600 min/wk), moderate (MET, 600-1,499 min/wk), and high (MET, ≥1,500 min/wk) levels.[32,33]

Smoking status was classified into two categories: ever smokers (current users and those who used to smoke in the past) and never smokers.

Statistical analysis

Statistical analysis was performed using the software package STATA (version 13; STATA, Inc, College Station, TX) with a significance level of $P < 0.05$ and a confidence interval (CI) of 95%. Continuous variables were assessed for normality using the Shapiro-Wilk test, with normally distributed variables presented as mean ± SD and nonnormal distributed variables presented as median (interquartile range). Categorical variables were expressed as percentages. Differences between the PCOS and non-PCOS groups were assessed using independent t tests or Pearson χ^2 tests for continuous and categorical

TABLE 1. *Baseline characteristics of participants in PCOS and non-PCOS control women*

Variable	PCOS (n = 348)	Non-PCOS control (n = 1,348)	P
Age, y[a]	30.0 (6.3)	33.2 (8.1)	**<0.001**
Weight, kg[a]	66.5 (12.9)	65.3 (11.9)	0.08
BMI, kg/m^2[a]	26.5 (5.0)	26.3 (4.7)	0.6
Education[b]			
Diploma and upper	203 (58.3)	773 (57.3)	0.7
Physical activity (moderate to high)[b]	99 (28.5)	402 (29.8)	0.6
Ever smoker[b]	6 (1.7)	44 (3.3)	0.1
Menarche age, y[a]	13.3 (1.5)	13.5 (1.3)	**0.01**
Parity[a]	1.7 (1.2)	1.8 (1.6)	0.1
Prevalence of chronic diseases[b]			
History of hypertension (yes/no)[b]	16 (4.6)	107 (7.9)	**0.03**
History of CVD (yes/no)[b]	0	13 (1)	0.06
History of prediabetes (yes/no)[b]	45 (13.0)	178 (13.6)	0.8
History of type 2 diabetes mellitus (yes/no)[b]	4 (1.1)	50 (3.7)	**0.01**
History of metabolic syndrome (yes/no)[b]	62 (17.8)	283 (21.0)	0.2
History of thyroid disorders (yes/no)[b]	10 (2.9)	56 (4.1)	0.3
History of cancer (yes, no)[b]	0	1 (0.07)	0.6
History of CKD (yes, no)[b]	5 (1.5)	41 (3.0)	0.1
Total testosterone, ng/mL[c]	0.5 (0.3–0.8)	0.3 (0.1–0.6)	**<0.001**
DHEAS, μg/dL[c]	159 (91.3–213.1)	119 (65.3–179.7)	**<0.001**
SHBG, nmol/L[c]	45.7 (34.2–60.2)	57.5 (43.5–80.7)	**<0.001**
Free androgen index[c]	1.1 (0.6–1.9)	0.6 (0.2–1)	**<0.001**
Androstenedione, ng/mL[c]	1.7 (1–2.3)	1.1 (0.9–1.7)	**<0.001**
Fasting plasma glucose, mg/dL[a]	86.7 (8.7)	89.9 (19.2)	**0.002**
2-h plasma glucose, mg/dL[a]	103.3 (27.1)	107.1 (36.2)	0.07

Bolded values show the groups that differ significantly, with a P-value of less than 0.05.
BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DHEAS, dehydroepiandrosterone sulfate; PCOS, polycystic ovary syndrome; SHBG, sex hormone binding globulin.
[a]Values are presented as mean (SD).
[b]Values are presented as number (percentage).
[c]Values are expressed as median (interquartile range).

data, respectively. Skewed distribution was addressed using the Mann-Whitney U test.

To determine whether PCOS status was associated with age at menopause, we used an accelerated failure time (AFT) survival regression model, which assumes a linear relationship between the logarithm of age at menopause and PCOS status, along with other covariates. This model assumes that the effect of a covariate is to multiply the hazard by some constant, and an AFT model assumes that the effect of a covariate is to accelerate or decelerate the life course of a disease by some constant.[34] We applied different AFT models with various parametric distributions and found that the Weibull distribution was best suited to time-to-menopause data based on Akaike information criteria.[35]

In AFT models, a positive coefficient indicates that there is a positive association between PCOS and age at menopause. This means that individuals with PCOS are expected to experience menopause at a later age compared with individuals without PCOS. Exponentiated regression coefficients correspond to acceleration factors or the ratio of mean survival times between the groups. Thus, a time ratio of 1.0 indicates no association between PCOS and time to menopause, with values less than 1.0 indicating a decrease in the time to menopause and values greater than 1.0 indicating a delay in development (1.0 is the null value). The event date was operationally defined as the occurrence of the desired outcome, namely, menopause. Subsequently, we calculated the proposed ANM, which we

TABLE 2. *Results of Weibull AFT survival regression model to explore the effect of PCOS status on age at natural menopause*

	Unadjusted model			Adjusted model[a]		
	Time ratio	95% CI	P	Time ratio	95% CI	P
PCOS	1.05	1.02–1.06	**<0.001**	1.03	1.01–1.06	**0.002**
Age at baseline	—			0.99	0.99–1.0	**0.01**
Age at menarche	—			1.01	0.99–1.01	0.5
History of hypertension	—			0.98	0.97–1.01	0.06
History of T2DM	—			0.97	0.95–0.99	**0.01**
Parity	—			0.99	0.99–1.01	0.08
OCP use	—			0.99	0.98–1.02	0.9
BMI	—			1.01	0.99–1.02	0.1
Education level (upper diploma)	—			0.99	0.97–1.01	0.1
Physical activity (moderate to high)	—			1.02	1.01–1.04	**0.01**
Smoking (yes)	—			0.98	0.96–1.02	0.5

Bolded values show the groups that differ significantly, with a P-value of less than 0.05.
BMI, body mass index; CI, confidence interval; OCP, oral contraceptive; PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus.
[a]Adjusted variables include age at baseline, age at menarche, history of hypertension, history of T2DM, parity, OCP use, BMI, education level, physical activity, and smoking.

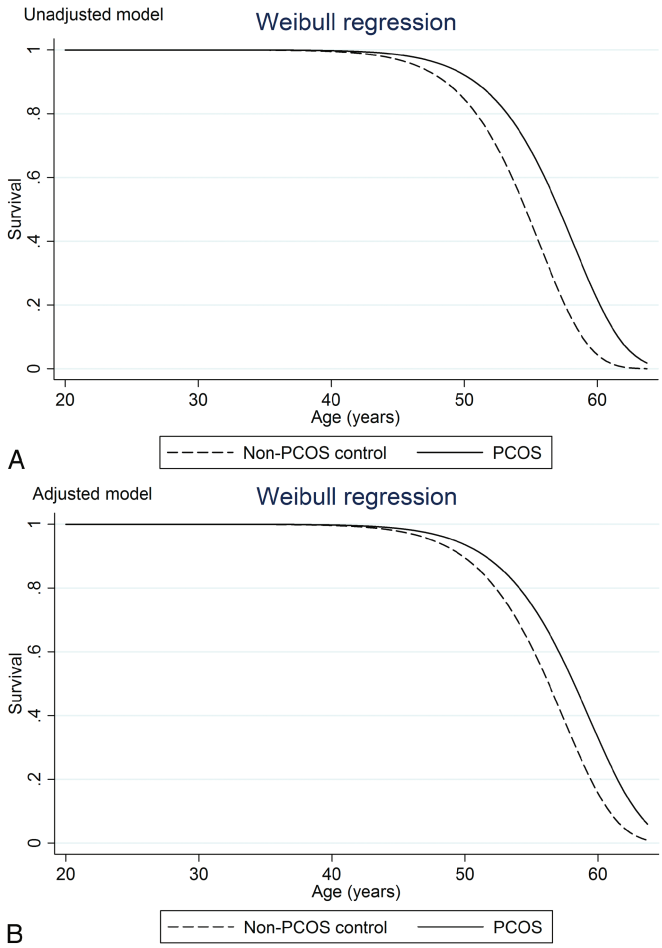

FIG. 2. Survival function plot (**A**) unadjusted and (**B**) adjusted model for ANM based on PCOS status. Adjusted variables include age at entrance, age at menarche, history of hypertension, history of T2DM, parity, OCP use, BMI, education level, physical activity, and smoking. ANM, age at natural menopause; BMI, body mass index; OCP, oral contraceptive; PCOS, polycystic ovary syndrome.

consistently denoted as ANM throughout this article. The survival time in the study was determined either by the attained age at menopause or, if menopause did not occur during the follow-up period, by the attained age at last available follow-up. Women who did not experience menopause during the study were considered censored, and their data were recorded until the end of the study or until the last follow-up point, whichever came first.

Unadjusted and adjusted AFT regression models were both considered. Variables with a P value <0.2 in the univariate analysis were added to the final multivariate models to control for the effects of confounding variables. The confounding impact of age at menarche, age at baseline, parity, oral contraceptive (OCP) use, BMI, education status, physical activity, smoking status, diabetes mellitus, and hypertension at baseline were controlled, and time ratios along with 95% CIs were reported.

RESULTS

The baseline characteristics of the study groups, including PCOS and non-PCOS controls, are presented in Table 1. A total of 348 women (20.5%) had PCOS, whereas 1,348 women (79.5%) were in the non-PCOS control group. Women with PCOS were significantly younger than non-PCOS controls (30.0 ± 6.3 vs 33.2 ± 8.1 y, $P < 0.001$) and had an earlier menarche age (13.3 ± 1.5 vs 13.5 ± 1.3 y, $P = 0.01$). The mean (SD) BMI was 26.5 ± 5.0 and 26.3 ± 4.7 kg/m^2 in PCOS and non-PCOS control groups, respectively. Women with PCOS had higher serum concentrations of TT, DHEAS, FAI, and A4 and lower concentrations of SHBG compared with non-PCOS controls (all $P < 0.001$).

A median follow-up of 18.9 years (interquartile range, 15.5-20.3 y) and 16.0 years (interquartile range, 11.0-19.5 y) for PCOS and non-PCOS control women has been recorded, respectively ($P < 0.001$). At the end of follow-up, a lower percentage of women in the PCOS group reached menopause compared with non-PCOS controls (33.1% vs 51.3%, $P < 0.001$) (Fig. 1).

The association between PCOS status and the ANM, estimated by the Weibull AFT model, is shown in Table 2. The unadjusted AFT survival model showed a significant positive association between PCOS and ANM; the ratio of the mean survival times between the groups was 1.05 (95% CI, 1.02-1.06; $P < 0.001$), indicating a delay in ANM. Our results remained significant even after adjustments, that is, age at baseline, age at menarche, history of hypertension, history of T2DM, parity, OCP use, BMI, education level, physical activity, and smoking,

indicating that for women with PCOS, the mean time to natural menopause increases by approximately 3% (95% CI, 1.01-1.06; $P = 0.002$). To illustrate the clinical implications of this finding, we can use an example. If we assume that the mean age of menopause for individuals without PCOS is 50, then applying the time ratio of 1.03 for PCOS status, we would expect an individual with PCOS to experience menopause at approximately 51.5 years of age (50×1.03). This suggests that the expected age at menopause for an individual with PCOS is approximately 3% later compared with an individual without PCOS, while holding other covariates constant.

Moreover, survival curves based on AFT regression models were plotted in Figure 2. As shown in the figure (for both unadjusted and adjusted models), PCOS was associated with higher probability of not reaching menopause compared with non-PCOS controls.

DISCUSSION

The findings from this 20-year population-based prospective study revealed that PCOS is associated with later age at menopause, compared with non-PCOS controls. This result remained significant even after adjusting for potential confounders.

Previous studies investigating the age of menopause in women with PCOS have reported inconclusive results, mainly because of methodological issues such as estimating age at menopause based on serum concentration of AMH instead of exact menopausal age, different statistical approaches, recall bias in retrospective studies, nonpopulation-based designs, low sample sizes, and failure to adjust for important confounders.[8,12-19] Several studies have calculated reproductive lifespan and age at menopause in women with PCOS based on the AMH concentrations or the antral follicle count earlier in life.[8,12-14,19] To the best of our knowledge, Mulders et al[14] (2004) conducted the first longitudinal study and demonstrated that the decline in AMH overtime is less pronounced in PCOS patients identified based on the Rotterdam criteria compared with controls. It is worth noting that the cohort participants were nonfertile women attending a fertility clinic, and thus the results may not be generalizable to the general population. Another study conducted among participants of TLGS estimated the reproductive lifespan of PCOS patients using AMH and found it to be extended on average by 2 years beyond that of women with ovulatory menstrual cycles (51 vs 49 y).[8] In a subsequent study from the same database but with a longer follow-up duration, a fractional polynomial regression model (instead of a linear regression model) was used to provide a nonlinear ANM prediction with a precise estimation that can be more generalizable to other settings. This study showed that AMH levels in women with PCOS are two to three times higher, and the estimated mean age at menopause is significantly longer than normal controls (49.7 y in PCOS vs 51.4 y in controls).[12] Both studies on participants from TLGS identified PCOS using National Institutes of Health criteria, which could be associated with missing mild cases of PCOS. A nested case-control study within the prospective cohort study on women aged 35 to 44 years showed that lower AMH levels were significantly associated with a higher risk of natural menopause before the age of 45 years. Significant associations between AMH and early menopause were observed in various subgroups of women, including those with and without a history of infertility, smoking, and menstrual irregularity. However, it should be noted that this study had several limitations, such as the nonlongitudinal design, the lack of measuring AMH in women younger or older than 35 years, and low statistical power because of a limited number of participants with AMH measurements.[19] In contrast, a retrospective cohort study on a large population of infertile patients with PCOS did not support the hypothesis of prolongation of the reproductive lifespan for PCOS women, despite the increased number of oocytes in the fourth decade. It is important to note that this discrepancy can be explained by variations in the study design and population because it had a retrospective design, which could lead to recall bias and included only infertile women.[13]

Although proposed models of age at menopause based on the AMH levels have shown satisfactory reliability, they may not be as accurate as actual menopausal age because of potential variations caused by hormonal assay methods.[36] In addition, because AMH levels decline at different rates among women,[37] using AMH measurements as a proxy for determining menopausal age can lead to inaccurate results. Several studies have compared the actual age of menopause between PCOS patients and healthy control groups, with conflicting results.[15-18] For example, data collected from hospital records of more than 300 British women diagnosed with PCOS by histopathologic criteria could not detect a significant difference in menopausal age in women with PCOS compared with the control group. However, it should be noted that the majority of these women had undergone ovarian surgery, including wedge resection, which could diminish their ovarian reserve and accelerate their menopausal age.[16] In contrast, a prospective population-based study of women aged 40 to 74 years undergoing mammography in Sweden showed that PCOS was associated with delayed menopause. They observed that the crude ANM was highest for women with a premenopausal diagnosis of PCOS (56 y) compared with those without such a history (52-53 y).[15] Although a cross-sectional study conducted on Sweden women in 1992 demonstrated a higher menopausal age in women with PCOS diagnosed based on the histopathologic criteria compared with age-matched controls,[18] the 21-year follow-up of that cohort and their age-matched controls showed no difference in menopausal age between women with PCOS reevaluated by Rotterdam criteria and non-PCOS controls.[17] However, this study had some methodological problems such as selection bias because it recruited a large number of cases undergoing ovarian surgery like wedge resection, which could lead to a decrease in the ovarian reserve.

The result of the adjusted AFT model revealed that the expected age at menopause for an individual with PCOS would be approximately 3% later compared with an individual without PCOS. It suggests that women with PCOS may experience menopause slightly later than those without PCOS, although the magnitude of the difference may not be clinically significant. Therefore, further longitudinal studies on different populations

with large sample sizes considering other confounding variables are required to gain a better understanding of the topic and to draw more definitive conclusions.

The major strength of this study was its design as a large population-based prospective study with a long follow-up, using an AFT regression model. The association between PCOS and age at menopause has been described by several approaches in the literature. Although the Cox proportional hazards model is widely used, AFT models are often more valid and exhibit better fitness under similar conditions. They also do not require a proportional hazards assumption.[38] Because the present study assessed androgens and ovarian morphology in all participants, regardless of menstrual pattern, it was unlikely to miss any hyperandrogenemic or polycystic ovary morphology participants. Intra-assay variability of the collected data was also likely to be minimal, as all laboratory measurements were performed in the study's research laboratory. The participants were followed at 3-year intervals on average and asked about their menstrual cycles. However, the study had some limitations that need to be addressed before interpreting of the results. First, although the diagnosis of menopause relied on self-reporting using the WHO criteria, this method may have some limitations, especially for women with PCOS who may have irregular or prolonged menstrual cycles and may find it more difficult to figure out when their cycles have permanently ceased. This could lead to some misclassification of menopausal status and age at menopause in our study, which can affect the accuracy of our findings. However, self-reported menopause has been shown to have high agreement with FSH levels and clinical diagnosis of menopause in previous studies.[39,40] It should also be noted that none of the participants were menopausal at the baseline visit, and short follow-up intervals of the TLGS (average 3 y) minimized recall bias for estimating age at menopause. Second, PCOS patients were younger than the control group, but age was controlled as a confounding variable in the adjusted models. Third, we attempted to control our results for several potential confounders through statistical adjustments, but residual confounding may still exist and affect our findings. For example, age at menopause can be influenced by genetic characteristics, socioeconomic status, ethnicity, and lifestyle factors, which were not adjusted for in this study because of data unavailability. These factors may confound or modify the association between PCOS and age at menopause and should be considered in future studies. Moreover, we lacked data on maternal age at menopause, which is an important variable that could have been adjusted for if it had been collected. Therefore, we urge caution in interpreting our findings.

CONCLUSIONS

This study indicates that age at menopause is significantly associated with PCOS in women. Our study findings may have implications for the fertility and reproductive health of women with PCOS. However, further large longitudinal studies on diverse populations accounting for other relevant confounders are still needed to provide data on the actual difference in age at menopause and to elucidate the underlying mechanisms of this association.

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REFERENCES

1. Utian WH. The International Menopause Society menopause-related terminology definitions. *Climacteric* 1999;2:284-286. doi: 10.3109/13697139909038088
2. Burger HG, Dudley EC, Hopper JL, et al. Prospectively measured levels of serum follicle-stimulating hormone, estradiol, and the dimeric inhibins during the menopausal transition in a population-based cohort of women. *J Clin Endocrinol Metab* 1999;84:4025-4030. doi: 10.1210/jcem.84.11.6158
3. Burger HG, Dudley EC, Hopper JL, et al. The endocrinology of the menopausal transition: a cross-sectional study of a population-based sample. *J Clin Endocrinol Metab* 1995;80:3537-3545. doi: 10.1210/jcem.80.12.8530596
4. Broer SL, Broekmans FJ, Laven JS, Fauser BC. Anti-Müllerian hormone: ovarian reserve testing and its potential clinical implications. *Hum Reprod Update* 2014;20:688-701. doi: 10.1093/humupd/dmu020
5. Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. *Endocr Rev* 2009;30:465-493. doi: 10.1210/er.2009-0006
6. Depmann M, Eijkemans MJ, Broer SL, et al. Does AMH relate to timing of menopause? Results of an individual patient data meta-analysis. *J Clin Endocrinol Metabol* 2018;103:3593-3600. doi: 10.1210/jc.2018-00724
7. Hudecova M, Holte J, Olovsson M, Sundström Poromaa I. Long-term follow-up of patients with polycystic ovary syndrome: reproductive outcome and ovarian reserve. *Hum Reprod* 2009;24:1176-1183. doi: 10.1093/humrep/den482
8. Tehrani FR, Solaymani-Dodaran M, Hedayati M, Azizi F. Is polycystic ovary syndrome an exception for reproductive aging? *Hum Reprod* 2010;25:1775-1781. doi: 10.1093/humrep/deq088
9. Piltonen T, Morin-Papunen L, Koivunen R, Perheentupa A, Ruokonen A, Tapanainen JS. Serum anti-Müllerian hormone levels remain high until late reproductive age and decrease during metformin therapy in women with polycystic ovary syndrome. *Hum Reprod* 2005;20:1820-1826. doi: 10.1093/humrep/deh850
10. Saxena R, Bjonnes AC, Georgopoulos NA, Koika V, Panidis D, Welt CK. Gene variants associated with age at menopause are also associated with polycystic ovary syndrome, gonadotrophins and ovarian volume. *Hum Reprod* 2015;30:1697-1703. doi: 10.1093/humrep/dev110
11. Ruth KS, Beaumont RN, Tyrrell J, et al. Genetic evidence that lower circulating FSH levels lengthen menstrual cycle, increase age at menopause and impact female reproductive health. *Hum Reprod* 2016;31:473-481. doi: 10.1093/humrep/dev318
12. Minooee S, Ramezani Tehrani F, Rahmati M, Mansournia MA, Azizi F. Prediction of age at menopause in women with polycystic ovary syndrome. *Climacteric* 2018;21:29-34. doi: 10.1080/13697137.2017.1392501
13. Kalra SK, Ratcliffe SJ, Dokras A. Is the fertile window extended in women with polycystic ovary syndrome? Utilizing the Society for Assisted Reproductive Technology registry to assess the impact of reproductive aging on live-birth rate. *Fertil Steril* 2013;100:208-213. doi: 10.1016/j.fertnstert.2013.02.055
14. Mulders AG, Laven JS, Eijkemans MJ, de Jong FH, Themmen AP, Fauser BC. Changes in anti-Müllerian hormone serum concentrations over time suggest delayed ovarian ageing in normogonadotrophic anovulatory infertility. *Hum Reprod* 2004;19:2036-2042. doi: 10.1093/humrep/deh373
15. Li J, Eriksson M, Czene K, Hall P, Rodriguez-Wallberg KA. Common diseases as determinants of menopausal age. *Hum Reprod* 2016;31:2856-2864. doi: 10.1093/humrep/dew264
16. Wild S, Pierpoint T, Jacobs H, McKeigue P. Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. *Hum Fertil (Camb)* 2000;3:101-105. doi: 10.1080/1464727002000198781
17. Schmidt J, Brännström M, Landin-Wilhelmsen K, Dahlgren E. Reproductive hormone levels and anthropometry in postmenopausal women with polycystic ovary syndrome (PCOS): a 21-year follow-up study of women diagnosed with PCOS around 50 years ago and their age-matched controls. *J Clin Endocrinol Metab* 2011;96:2178-2185. doi: 10.1210/jc.2010-2959

18. Dahlgren E, Johansson S, Lindstedt G, et al. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. *Fertil Steril* 1992;57:505-513. doi: 10.1016/S0015-0282(16)54892-4
19. Bertone-Johnson ER, Manson JE, Purdue-Smithe AC, et al. Anti-Müllerian hormone levels and incidence of early natural menopause in a prospective study. *Hum Reprod* 2018;33:1175-1182. doi: 10.1093/humrep/dey077
20. Azizi F, Rahmani M, Ghanbarian A, et al. Serum lipid levels in an Iranian adults population: Tehran Lipid and Glucose Study. *Eur J Epidemiol* 2003;18:311-319. doi: 10.1023/A:1023606524944
21. Ramezani Tehrani F, Behboudi-Gandevani S, Rostami Dovom M, et al. Reproductive assessment: findings from 20 years of the Tehran Lipid and Glucose Study. *Int J Endocrinol Metab* 2018;16(4 suppl):e84786. doi: 10.5812/ijem.84786
22. Ramezani Tehrani F, Montazeri SA, Hosseinpanah F, et al. Trend of cardio-metabolic risk factors in polycystic ovary syndrome: a population-based prospective cohort study. *PloS One* 2015;10:e0137609. doi: 10.1371/journal.pone.0137609
23. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004;81:19-25. doi: 10.1016/j.fertnstert.2003.10.004
24. Rosenfield RL. Clinical practice. Hirsutism. *N Engl J Med* 2005;353:2578-2588. doi: 10.1056/NEJMcp033496
25. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab* 2004;89:2745-2749. doi: 10.1210/jc.2003-032046
26. Carmina E, Dreno B, Lucky WA, et al. Female adult acne and androgen excess: a report from the multidisciplinary androgen excess and PCOS committee. *J Endocr Soc* 2022;6:bvac003. doi: 10.1210/jendso/bvac003
27. Hashemi S, Ramezani Tehrani F, Noroozzadeh M, Azizi F. Normal cut-off values for hyperandrogenaemia in Iranian women of reproductive age. *Eur J Obstet Gynecol Reprod Biol* 2014;172:51-55. doi: 10.1016/j.ejogrb.2013.09.029
28. Jonard S, Robert Y, Cortet-Rudelli C, Pigny P, Decanter C, Dewailly D. Ultrasound examination of polycystic ovaries: is it worth counting the follicles? *Hum Reprod* 2003;18:598-603. doi: 10.1093/humrep/deg115
29. Gifford R. Report of the national high blood pressure education program working group on high blood pressure in pregnancy. *Am J Obstet Gynecol* 2000;183:S1-S15. doi: 10.1067/mob.2000.107928
30. Eslami A, Lotfaliany M, Akbarpour S, Azizi F, Hadaegh F. Trend of cardiovascular risk factors in the older Iranian population: 2002-2014. *Geriatr Gerontol Int* 2018;18:130-137. doi: 10.1111/ggi.13154
31. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2013;36(Suppl 1):S67-S74. doi: 10.2337/dc14-S081
32. Manley AF, ed. Physical Activity and Health: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1996.
33. Delshad M, Ghanbarian A, Ghaleh NR, Amirshekari G, Askari S, Azizi F. Reliability and validity of the modifiable activity questionnaire for an Iranian urban adolescent population. *Int J Prev Med* 2015;6:3. doi: 10.4103/2008-7802.151433
34. Wei LJ. The accelerated failure time model: a useful alternative to the Cox regression model in survival analysis. *Stat Med* 1992;11(14-15):1871-1879. doi: 10.1002/sim.4780111409
35. Moran JL, Bersten AD, Solomon PJ, et al. Modelling survival in acute severe illness: Cox versus accelerated failure time models. *J Eval Clin Pract* 2008;14:83-93. doi: 10.1111/j.1365-2753.2007.00806.x
36. Fu YX, Wang H, Hu T, Wang FM, Hu R. Factors affecting the accuracy and reliability of the measurement of anti-Müllerian hormone concentration in the clinic. *J Int Med Res* 2021;49:3000605211016161. doi: 10.1177/030006052110161
37. Freeman EW, Sammel MD, Lin H, Boorman DW, Gracia CR. Contribution of the rate of change of antimüllerian hormone in estimating time to menopause for late reproductive-age women. *Fertil Steril* 2012;98:1254-9.e1-2. doi: 10.1016/j.fertnstert.2012.07.1139
38. Orbe J, Ferreira E, Núñez-Antón V. Comparing proportional hazards and accelerated failure time models for survival analysis. *Stat Med* 2002;21:3493-3510. doi: 10.1002/sim.1251
39. Colditz GA, Stampfer MJ, Willett WC, et al. Reproducibility and validity of self-reported menopausal status in a prospective cohort study. *Am J Epidemiol* 1987;126:319-325. doi: 10.1093/aje/126.2.319
40. Phipps AI, Ichikawa L, Bowles EJ, et al. Defining menopausal status in epidemiologic studies: a comparison of multiple approaches and their effects on breast cancer rates. *Maturitas* 2010;67:60-66. doi: 10.1016/j.maturitas.2010.04.015