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Higher menopausal age but no differences in parity in women with polycystic ovary syndrome compared with controls

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Abstract

Introduction: To address the question of whether women with polycystic ovary syndrome (PCOS) reach menopause later than age-matched controls, we conducted a follow-up cohort study of women with well-characterized PCOS that was diagnosed 24 years ago. The hypothesis was that women with PCOS would reach menopause later than non-PCOS women. Parity during these 24 years was also studied.

Material and methods: Twenty-seven women diagnosed with PCOS in 1992 (mean age 29.5 years) were re-examined in 2016 (mean age 52.4 years). Randomly selected women, n = 94 (mean age 52.4 years), from the same geographic area included in the World Health Organization MONICA study, Gothenburg, Sweden, served as controls.

Results: The mean menopausal age in women with PCOS was higher than in controls (53.3 ± 2.2 years vs 49.3 ± 3.5 years, $P < 0.01$). Serum-follicle stimulating hormone levels were lower in the PCOS women than in controls (31.0 ± 28.1 IU/L vs 52.3 ± 37.7 IU/L, $P = 0.01$). There was no difference in parity between women with PCOS (1.9 ± 1.3 children, range 0-4) and controls (1.7 ± 1.0, range 0-4 children).

Conclusions: Women with PCOS reached menopause 4 years later and had lower serum-follicle stimulating hormone compared with age-matched controls. Neither parity nor nulliparity differed between women with PCOS and controls.

KEYWORDS
follicle stimulating hormone, menopausal age, parity, polycystic ovary syndrome

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, with a prevalence of 5%-10% depending on what diagnostic criteria are applied.[1-3] It is characterized by oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries; where according to the Rotterdam criteria, two of three criteria should be present for PCOS diagnosis.[4]

The syndrome is associated with insulin resistance, hypertension and diabetes.[5-10] Our group was the first to show, in a study from 1992,[11] that women with PCOS exhibit a risk factor profile for cardiovascular disease. The risk factor model predicted a seven-fold increased risk of myocardial infarction. However, later studies on morbidity in women with PCOS have not been able to confirm an increased risk of cardiovascular disease.[7,9,12,13]

It has been speculated that women with PCOS have inherent cardioprotective factors and that these may be related to altered

hormonal levels later in life. It is well known that the incidence of cardiovascular disease events increases after menopause in women in general,[14] and also after premenopausal prophylactic oophorectomy.[15] Thus, one hormonal protective factor among PCOS women could be the higher menopausal age, causing a delayed decrease in estrogen levels that may protect against cardiovascular disease.

Menopause is defined as the point in time when there has been no menstrual period for 1 year and no other biological or physiological cause can be identified. Consequently, menopause has to be defined retrospectively. Physiologically, menopause occurs when the number of ovarian follicles declines below a critical threshold (estimated to be ~1000 follicles) and ovulation ceases.[16] Reproductive aging starts prior to birth and continues until menopause, when the primary mechanism is the depletion of the ovarian pool of follicles. The age of menopause varies between women and it is unclear whether this difference is due to the original number of follicles or differences in the depletion of the follicles. Women with PCOS have higher anti-Müllerian hormone (AMH) levels as compared with controls,[17] and the AMH levels are highly correlated with antral follicle count on ultrasound and can be used as a surrogate for follicle number.[18] Thus, it is biologically likely that women with PCOS would reach menopause later. The age of menopause in the general population is around 51 years.[19]

To address the question of whether women with PCOS reach menopause later than age-matched controls, we conducted a follow-up cohort study of women with well-characterized PCOS that was diagnosed 24 years ago. We hypothesized that women with PCOS would reach menopause later than non-PCOS women. Parity during these 24 years was also studied.

2 | MATERIAL AND METHODS

2.1 | Women with PCOS

In 1992, 33 women attending Sahlgrenska University Hospital for infertility or hirsutism, were diagnosed with PCOS according to the National Institute of Health criteria.[20] They were then invited and agreed to participate in a study regarding hormonal treatment for hirsutism, including clinical examination, blood sampling and structured interviews before the intervention.[21]

A follow-up study was carried out in 2016. Of the 33 women with PCOS, five had died and one declined to participate. Thus, 27 PCOS women, at that time aged 42-63 years, were included. Of these, 25 participated in all parts of the follow-up study and two completed the interviews only.

Since all the women in the PCOS group had been previously diagnosed using National Institute of Health criteria, all of them also fulfilled the Rotterdam criteria.[4]

2.2 | Controls

A randomly selected population sample of women participated in the World Health Organization study MONItoring of trends and

Key message

In this 24-year prospective controlled study of well-characterized polycystic ovary syndrome women, women with polycystic ovary syndrome were found to have a 4-year delay in menopausal age and similar parity as a random population sample of women.

determinants for CArdiovascular disease (MONICA) study in 1995, Gothenburg, Sweden.[22] They were re-examined with a physical examination and similar questionnaires in 2008, with a participation rate of 65%.[23] Controls for the present study were recruited from the women participating in the 2008 follow up. A group-matching model based on age was used. Of 317 women in the age group 39-78 years, 95 women were selected as a control group. One woman was excluded due to a testosterone level above the reference interval at that time, leaving a final control group of 94 women.

2.3 | Anthropometry

Height was measured to the nearest 0.5 cm. Body weight was measured wearing only underwear to the nearest 0.5 kg. For the two PCOS women who did not participate in the clinical investigation, self-reported weight and height were used. Body mass index (BMI) was calculated as bodyweight divided by height squared (kg/m^2). Waist and hip circumference were measured to the nearest cm in the standing position over the umbilicus and the maximum circumference over the buttocks, respectively, and the waist-to-hip ratio was calculated.

2.4 | Structured medical history including menopausal age

At the clinical examination, data were retrieved on current and previous diseases, medication, parity and if and when the women estimated that the menopause (the last menstrual bleeding) had occurred. Menopause was defined as the last menstrual bleeding followed by 1 year of amenorrhea and thus was defined retrospectively. Women using hormone replacement therapy or oral contraceptives were categorized as using systemic hormone therapy.

Similar protocols were used for the controls and the PCOS women. The women with PCOS were also asked whether they had had infertility treatment at any time (yes or no).

2.5 | Biochemical assays

Fasting venous blood samples were taken between 07:30 and 08:30 hours in the supine position after at least 15 minutes of rest. The blood samples were drawn on cycle days 7-9 in the control group but not timed with the menstrual cycle in the women with

PCOS. The analyses were performed at the accredited (SWEDAC ISO 15189) Laboratory for Clinical Chemistry, Sahlgrenska University Hospital.

Chemiluminescent microparticle immunoassays (Architect i2000SR) were used for serum-follicle stimulation hormone (S-FSH) and serum-luteinizing hormone (S-LH), with detection limits of 0.05 and 0.1 IU/L for FSH and LH, respectively. The coefficients of variation were 6%-9% and 7%-11% for the FSH and LH analyses, respectively. There were no changes to the immunoassay methods between 2008 (controls) and 2016 (PCOS). A level of S-FSH >50 IU/L was considered postmenopausal, according to Burger et al.[24]

For all hormonal analysis, women using systemic hormone therapy were excluded from the statistical analysis.

2.6 | Statistical analyses

Mean value, median, SD and range were calculated with conventional methods. SPSS Statistics version 25 (IBM Corp., Released 2017, IBM SPSS Statistics for MAC, Armonk, NY, USA) was used for the analyses. Intergroup comparisons of continuous variables that were normally distributed were calculated with the independent samples t test. Data that were not normally distributed were tested with the Mann-Whitney U test. Categorical comparisons were calculated using Fisher's exact t test. To test whether BMI was a factor associated with parity number, linear regression was used.

Sample size calculation (α = 0.05, power = 0.80) was performed. To detect a difference in menopausal age of 2 years (with 3 years SD) would require a total sample size of 74. To detect a difference in parity of 0.5 (with 1 SD) would require a total sample size of 128.

2.7 | Ethical approval

The study was approved by the Regional Ethical Review Board in Gothenburg (reg. nos. 221-16, 088-06 and T282-11), and all the women gave their written informed consent.

3 | RESULTS

Background characteristics of the PCOS women and controls are shown in Table 1.

The mean age of women with PCOS and controls was similar (52.4 years), with age ranges of 42-63 years and 39-62 years, respectively.

Women with PCOS had higher BMI (31 ± 7 vs 26 ± 4 kg/m^2), bodyweight (86 ± 21 vs 70 ± 11 kg), waist circumference (102 ± 18 vs 87 ± 11 cm), hip circumference (113 ± 15 vs 104 ± 9 cm), and waist/hip ratio (0.90 ± 0.12 vs 0.83 ± 0.06) than the controls.

The menopausal age (mean ± SD/median [range]) in women with PCOS was higher than in controls; 53.3 ± 2.2/53.0 (50-56) vs 49.3 ± 3.5/50.0 (40-55) (P < 0.01). Mean S-FSH levels were lower in the women with PCOS (31.0 ± 28.1 IU/L) compared with controls (52.3 ± 37.7 IU/L) (P = 0.01) (Table 2). The proportion of S-FSH levels

TABLE 1 Anthropometric data and smoking habits in women with polycystic ovary syndrome (PCOS) and controls. Mean ± SD is given

	PCOS (n = 27)	Controls (n = 94)	P-value
Age (years)	52.4 ± 5.4	52.4 ± 6.3	0.676
Body weight (kg)	86.3 ± 21	70.1 ± 11	**<0.001**
Height (cm)	168 ± 6	166 ± 6	0.130
Body mass index (kg/m^2)	30.7 ± 7.4	25.5 ± 3.9	**0.001**
Waist circumference (cm)	101.7 ± 18.0	86.6 ± 1.6	**<0.001**
Hip circumference (cm)	112.9 ± 15.3	103.7 ± 8.9	**0.004**
Waist/hip ratio	0.90 ± 0.12	0.83 ± 0.06	**0.016**
Current smoker, n (%)	3 (11)	9 (10)	1.000
Never smoker, n (%)	12 (44)	49 (53)	0.513

P-values that are statistically significant are shown as bold.

above 50 IU/L (Table 2) was 22% among the women with PCOS and 55% among the controls (P < 0.01).

In women with PCOS, 37% (n = 10) stated that they were postmenopausal, compared with 57% (n = 54) of the controls (ns). In all, 44% of PCOS women stated that they were premenopausal, compared with 26% of controls.

Five of the women with PCOS and 16 of the controls were not certain whether they were menopausal, and three of the women in the PCOS group and two in the control group who claimed to be postmenopausal, could not report their actual age at menopause. The causes were hysterectomy, bilateral oophorectomy, long periods of amenorrhea, hormonal intrauterine devices or systemic hormone therapy. To check whether BMI was associated with menopausal age, a linear regression was performed, showing no association (P = 0.458).

There was no difference in parity between women with PCOS and controls (Table 2). The distribution of parity (0-4) is shown in Figure 1. Nulliparity was similar in both groups. A tendency towards more children was seen in the PCOS group; 33% of the women with PCOS had more than 2 children, compared with 22% in the control group (P = 0.212). At least 50% of the women in the PCOS group had had infertility treatment before one or more of their pregnancies. No data were available on infertility treatment in the control group.

4 | DISCUSSION

The main finding of the present study was that women with PCOS reached menopause 4 years later than their age-matched controls. S-FSH levels and the proportion of women with S-FSH >50 IU/L were also lower in women with PCOS. Neither parity nor nulliparity differed between PCOS and controls.

TABLE 2 Gonadotropin levels, menopausal age and parity in women with polycystic ovary syndrome (PCOS) and controls. Mean ± SD is given and percentages (%) in parentheses. Median and range is also given

	PCOS (n = 27)		Controls (n = 94)		
	Mean (SD)	Median/range	Mean (SD)	Median/range	P-value
FSH, IU/L	31.0 ± 28.1	29.0/2.03-105	52.3 ± 37.7	58-3/2.5-215	**0.010**
LH, IU/L	14.3 ± 9.2	14.6/1-32	20.3 ± 12.8	22.1/1-79	**0.040**
FSH >50 IU/L, n (%)	5 (21.7)		47 (55.3)		**0.005**
Menopausal age by history, years	53.3 ± 2.2	53.0/50-56	49.4 ± 3.5	50.0/40-55	**0.003**
Parity, n (%)	1.85 (1.29)	2/0-4	1.66 (1.05) n = 93	2/0-4	0.475
Nulliparity, n (%)	5 (18.5)		18 (19.4)		1.000
Hysterectomy, n (%)	4 (14.8)		5 (5.3)		0.111
Bilateral SOE, n (%)	1 (3.7)		1 (1.1)		0.108
Systemic hormone therapy, n (%)	2 (7.4)		9 (9.6)		1.000
Hormonal IUD, n (%)	2 (7.4)		9 (9.6)		1.000

P-values that are statistically significant are shown as bold.
For PCOS, n = 27, except for FSH and LH (n = 23) and menopausal age (n = 7).
For controls, n = 94 except for FSH and LH (n = 84) and menopausal age (n = 52).
FSH, follicle stimulating hormone; IUD, intrauterine device; LH, luteinizing hormone; SOE, salpingo-oophorectomy.
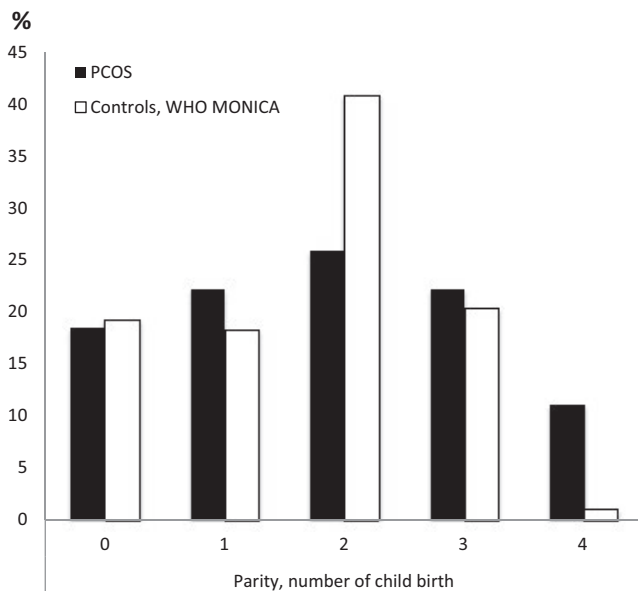

FIGURE 1 Percentage of women with childbirth parity, for women with polycystic ovary syndrome (PCOS) (n = 27) and controls (n = 93) from the World Health Organization (WHO) MONItoring of trends and determinants for CArdiovascular disease (MONICA)

Few previous studies have focused on menopausal age in women with PCOS. One study, including more than 300 British women, and with data obtained from general practice records and questionnaires, could not find a difference in menopausal age in women with PCOS.[25] However, that study had a substantial non-response rate; only 38% of the initial PCOS cohort answered the questionnaire at follow-up in the study.[23] The majority of the women had undergone ovarian surgery, including wedge resection, which reduced the ovarian reserve and had plausible secondary consequences for menopausal age.[23] A recent epidemiological study of 61 936 women undergoing mammography in Sweden investigated whether common self-reported diseases affected the age of the natural menopause. It was found that a self-reported PCOS diagnosis was independently associated with delayed menopause, which is in line with the present study.[19] However, neither of these studies reported on gonadotropin levels.[19,25]

There have been attempts to calculate the menopausal age of women with and without PCOS based on AMH levels earlier in life.[17,26,27] The postulated menopausal age of women with PCOS, based on AMH, was approximately 2 years later than that of controls.[27] This is in line with our findings of the verified menopausal age, based on medical history and biochemistry.

Polycystic ovary syndrome can only be diagnosed during the reproductive years. Hence, estimations of outcomes later in life require long-term follow-up studies of well-characterized populations. All the women with PCOS included in this study were diagnosed 24 years ago, at the age of 19-38 years.

Already in 1992, our research group suggested a higher menopausal age in women with PCOS when studying another cohort of

women with PCOS.[3] The 21-year follow up of that cohort and their age-matched controls[5] showed no difference in menopausal age. However, in the same study, the women with PCOS had lower S-FSH levels into their 70s, but their S-estradiol levels were similar to those of the non-PCOS group. One explanation could be that the majority of the women with PCOS from that study[5] had undergone ovarian surgery (including wedge resection, the treatment of choice at that time). Ovarian surgery leads to a decrease in the ovarian reserve, which could lead to an earlier menopausal age. For this reason, this result cannot be generalized to women with PCOS who have not undergone ovarian surgery, as in the majority of the women with PCOS in the present study.

On average, the early menopausal transition starts at age 47 and the late transition with the rise in FSH usually starts at age 49.[24] The age of menopause has been shown to be around 51 years in women in the general population.[28,29] During the menopausal transition, S-estradiol falls with a concomitant increase in S-FSH.[24,30] Regarding S-FSH, Burger et al[24] showed that the levels increased 5-fold over 3 years, with mean levels around 18 IU/L at 1.5 years before menopause to around 48 IU/L at the time of menopause in healthy women. The mean S-FSH level was used in the present study for evaluation of the menopausal transition. The control group had a higher S-FSH mean (50 IU/L) compared with the PCOS women (32 IU/L). According to Burger et al,[30] an S-FSH value of around 50 IU/L was associated with the time around menopause and the year after it. This result also supports the hypothesis that women with PCOS reach menopause later than women without PCOS.

The later menopausal age in women with PCOS could not be explained by smoking, which is a confounder and leads to an earlier menopause.[31] Smoking habits, both current and previous, were similar in the women with PCOS and controls in the present study.

The women with PCOS in this study had higher bodyweight than the controls. In PCOS, independently of obesity, ovarian function seems to normalize during the late reproductive age, with an increased number of ovulatory cycles and more regular cycles.[32-34] Whether obesity is a factor that affects the menopausal age is still unclear, with diverging results from different studies, as reviewed by Al-Safi and Polotsky.[35] In the present study, no association was seen between BMI and menopausal age.

A delayed menopausal age in women with PCOS is not only of reproductive interest.

It is tempting to believe that the sustained ovarian hormone levels may be protective against, or play a role in the absence of, increased cardiovascular events found in the previously studied cohort of women with PCOS.[9] Further confirmatory and larger studies are needed in this field.

Another finding of the present study was that women with PCOS had similar parity and nulliparity levels to controls. This is important knowledge for young women diagnosed with PCOS, who may worry about their future reproductive capacity. None of the women with PCOS in the current study had undergone wedge resection or ovarian drilling.

The present results are similar to the results from a Finnish study where women with symptoms from both oligo-amenorrhea and hirsutism were compared with women without either of these symptoms at the age of 44.[36] The Finnish study showed no difference in having at least one child. In contrast to the present study, women with oligo-amenorrhea and hirsutism in the Finnish study had a smaller family size than women without symptoms did.[36] The women in the current study had a tendency towards a bigger family size, although this was not statistically significant (Figure 1. One reason for the contrasting results could be that the present women with PCOS were recruited from a hospital setting, which enabled them to get help with possible infertility problems. Indeed, at least 50% of the women with PCOS had had infertility treatment before one or more of their pregnancies. It is known that BMI is a predictor of treatment resistance in pharmacological induction of ovulation.[37] With this in mind it is encouraging to see the good results on both spontaneous and assisted pregnancies in the PCOS group, despite the higher average BMI. No data were available regarding the proportion of infertility treatment in the control group.

Limitations of the present study were the small sample size of the groups and the evaluation of the controls some years before the investigation of the PCOS women.[23] Some of the women had become menopausal several years ago. Thus, there is a possibility for recall bias, both in women with PCOS and women in the control group. A strength of the study was that both the women with PCOS and the controls came from the same area (Gothenburg with surroundings) and there is no reason to believe that secular trends affected the results. Furthermore, the same laboratory was used for all the biochemical variables used in the study. The diagnosis of PCOS in 1992 was established according to National Institute of Health criteria and all the women with PCOS met the Rotterdam criteria when re-evaluated 24 years later in 2016. Thus, the establishment of the diagnosis of PCOS during the reproductive period of their life and followed until postmenopausal ages is unique and should be considered a strength.

5 | CONCLUSION

Women with PCOS reached menopause 4 years later and had lower S-FSH levels than their age-matched controls. Neither parity nor nulliparity differed between the groups.

CONFLICT OF INTEREST

The authors have nothing to declare.

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