

An overview of polycystic ovary syndrome in aging women

Özlem Çelik¹, Mehmet Faruk Köse²

¹Department of Internal Medicine, Division of Endocrinology and Metabolism, Acıbadem University Faculty of Medicine, İstanbul, Turkey

²Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Acıbadem University Faculty of Medicine, İstanbul, Turkey

Abstract

The manifestations of polycystic ovary syndrome (PCOS), a ubiquitous reproductive disorder, may vary significantly depending on the severity of a number of endocrine and metabolic changes. Although no diagnostic criteria are presently available for PCOS for perimenopausal and menopausal women, the condition can still be suspected in case of a previous diagnosis of the condition, a chronic history of irregular menstrual cycles and hyperandrogenism, and/or polycystic ovarian morphology during the reproductive period. PCOS is associated with long-term health risks, including obesity, diabetes, hypertension, dyslipidemia, metabolic syndrome and cardiovascular risk factors during reproductive age, especially in patients possessing classic phenotypes. The aim of this review was to outline the available data about the impact of PCOS on long-term health risks after reproductive age in patients with PCOS. Previously, it was assumed that women with PCOS would be more prone to develop cardiometabolic diseases after reproductive age but current data suggest that in accordance with the healing in the phenotypic characteristics of PCOS, no deterioration appears to occur in cardiometabolic health in these patients. While there is substantial evidence for a greater prevalence of abnormal subclinical atherosclerotic markers among younger patients with PCOS, data for older women are insufficient. However, there is also support for an increased risk of endometrial cancer in PCOS patients. Extensive prospective cohort studies in which healthy controls as well as patients with defining PCOS phenotypes are observed and monitored from the early reproductive period into the late postmenopausal period should now be performed in order to clarify morbidities and mortality in aging women with PCOS. (J Turk Ger Gynecol Assoc 2021; 22: 326-33)

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Introduction

Polycystic ovary syndrome (PCOS) is the most frequently seen endocrine disorder among women of reproductive age, with a reported prevalence ranging between 5% and 20%, due to various diagnostic criteria employed (1-3). PCOS is a heterogeneous disorder defined by a combination of clinical or biochemical hyperandrogenism (HA), oligo-anovulation (OA) and polycystic ovarian morphology (PCOM) on ultrasound (4). Three sets of proposed diagnostic criteria are available for defining PCOS, produced by the National Institutes of Health (NIH), and the Rotterdam and AE-PCOS Society guidelines (5-7). In all three

sets, other mimicking entities, such as thyroid disorders, hyperprolactinemia, hypercortisolemia and congenital adrenal hyperplasia, must be excluded before a diagnosis of PCOS is made. According to the Rotterdam criteria, at least two of the following are required for a diagnosis of PCOS-OA, HA, or the presence of PCOM (6). Various phenotypes have been identified based on these diagnostic characteristics. Phenotype A, in which patients satisfy all three PCOS diagnostic criteria, is the most common form. Patients with HA and OA but without PCOM are classified as Phenotype B, and those with HA and PCOM but not OA are classified as phenotype C. Phenotype D is a non-hyperandrogenic form including OA and PCOM (8).



Address for Correspondence: Özlem Çelik

e.mail: ozlemcash@yahoo.com ORCID: orcid.org/0000-0002-7254-0757

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Women with PCOS may present with hirsutism, acne, irregular menses, and infertility during reproductive age. However, definition of PCOS in menopausal women is problematic. A previous history of OA, infertility, and HA have been employed in order to identify the phenotype for postmenopausal women in previous studies (9). PCOS is a life-long disorder entailing several long-term health risks (Figure 1). With increasing age, it was assumed that PCOS evolved from a reproductive disease to a more metabolic disorder including visceral obesity, dyslipidemia, diabetes mellitus (DM), hypertension (HT), metabolic syndrome (MS), cardiovascular diseases (CVD), and endometrial cancer (EC) (3). Limited evidence is available concerning the natural history of PCOS during the perimenopausal and menopausal period (10). This review discusses these changes and comorbidities after reproductive age in patients with PCOS in the light of the latest evidence.

Perimenopausal/menopausal transition in PCOS

Menopausal transition is a physiological process associated with aging and various associated hormonal and metabolic changes (11). Androgen levels remain stable or may even rise as menopause commences, while a marked decrease occurs in estrogen levels. Ovarian granulosa cells, the principal secretors of estradiol and inhibin, also decline. This reduced inhibition by estrogen and inhibin on gonadotropins results in increased secretion of these hormones. Antral follicle count

and ovarian volume decline with age, eventually becoming incapable of responding to the effects of follicle-stimulating hormone. As ovarian aging progresses, estrogen levels may be quite variable, with chaotic patterns. In general, menopausal transition is characterized by a gradual decrease in menstrual bleeding. However, some women do experience heavy or prolonged bleeding, which has always been assumed to be due to anovulatory cycles and prolonged exposure to unopposed estrogen. The propensity for anovulatory cycles may lead to endometrial hyperplasia or carcinoma, and uterine polyps. After sometimes years of menstrual irregularity, women eventually experience permanent cessation of menses.

PCOS can be difficult to diagnose during the perimenopausal period, since aging leads to alterations in all three diagnostic criteria. The PCOS phenotype improves with age, as defined by an increase in regular menstrual cycles and decreased ovarian volume and follicle numbers (9). The Endocrine Society guideline suggests that a presumptive diagnosis of PCOS in older women might be based upon an appropriately evidenced long-term history of OA and HA during reproductive age (12). Elting et al. (13) demonstrated that women with PCOS frequently gain regular menstrual cycles due to loss of follicles during ovarian aging. In another study older women with PCOS who gained regular menstruation were compared with individuals whose cycles became irregular. The findings of this study showed that a lower follicle count in patients with PCOS predicted the emergence of regular menstrual cycles

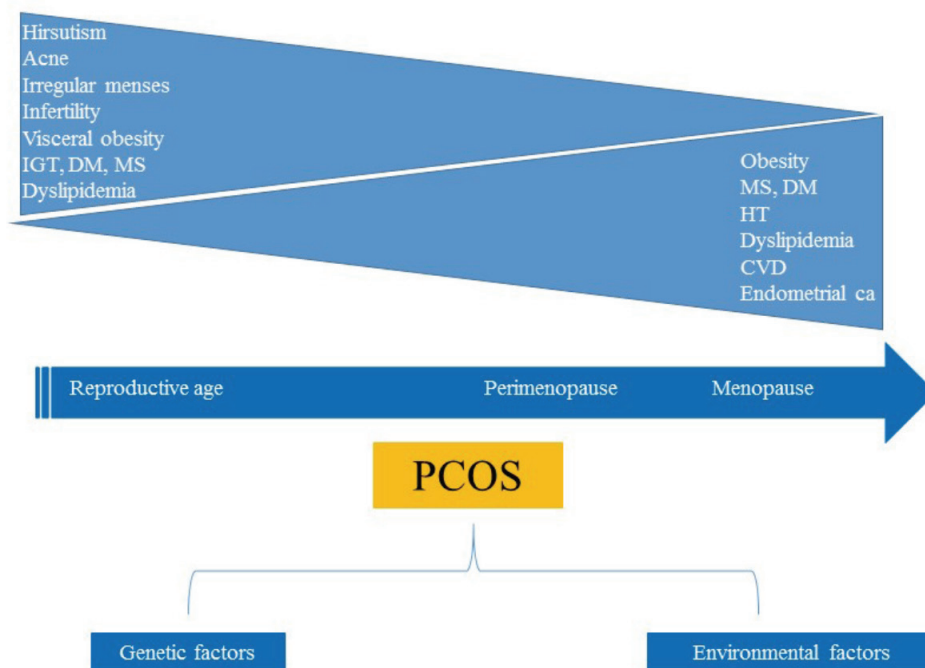


Figure 1. Clinical components of polycystic ovary syndrome throughout life

IGT: Impaired glucose tolerance, DM: Diabetes mellitus, MS: Metabolic syndrome, HT: Hypertension, CVD: Cardiovascular diseases, PCOS: Polycystic ovary syndrome

with age. This in turn confirmed that the regular menstrual cycles observed among older women with PCOS is principally due to a reduction in the follicle cohort size with ovarian aging (14). Alsamarai et al. (15) suggested that women with PCOS exhibited a less marked decrease in ovarian volume than healthy controls. A combination of age, and a decrease in log ovarian volume, follicle number, and testosterone (T) levels have been proposed for differentiating PCOS in women over 40 from healthy controls (15).

HA is of central significance in the pathophysiology of PCOS and is linked to anovulation, infertility and several metabolic diseases. Partial resolution of HA may be observed in the perimenopausal period among patients with PCOS due to ovarian and adrenal aging and reduced androgen production (10). In a study of 84 women with PCOS, Winters et al. (16) reported approximately 50% lower total T and non-dehydroepiandrosterone sulfate (DHEAS)-bound T-levels in the 45-47 age group compared to those in women in their 20s and 30s (16). Carmina et al. (17) followed-up 193 women, from a mean age of 22 to 43, and reported decreases of approximately 25% in T-levels and 30% in DHEAS levels. Ovarian size also decreased, by approximately 20%, in women with PCOS after long-term follow-up, and more ovulatory cycles were observed, indicating a milder disorder. Although the majority of women with mild HA eventually normalized, many others with the more severe phenotypes (A and B) remained hyperandrogenic (17). However, other authors have reported that overproduction of androgen levels in women with PCOS persisted even after menopausal transition (18). Markopoulos et al. (19) observed higher 17-hydroxyprogesterone, Δ 4-androstenedione (Δ 4A), DHEAS, total T, and free androgen index (FAI) levels and baseline lower sex hormone binding globulin levels in postmenopausal patients with PCOS compared to control subjects. These authors inferred from this that postmenopausal women with PCOS are exposed to higher androgen levels, both adrenal and ovarian, than individuals without PCOS (19). Pinola et al. (20) reported elevated serum androgen levels even in the postmenopausal period in women with PCOS. Calculated free T, Δ 4A and FAI were identified as the most accurate predictors of PCOS at all ages (20). Puurunen et al. (21) reported that basal androgen, with the exception of DHEA, either remained unchanged or else was slightly higher in pre- and post-menopausal women with PCOS, and that area under the curve levels were also higher. In another study, increased ovarian androgen levels were reported, together with adverse metabolic changes including impaired glucose tolerance (IGT) and chronic inflammation among premenopausal women with PCOS, and that these findings continued after the perimenopausal period. These results were described as emphasizing life-long health risks associated with PCOS (22). Hirsutism is more prevalent

in women with PCOS than in the normal healthy population, although data concerning acne and alopecia in these patients are lacking (23). Liang et al. (24) showed that androgens (TT and DHEAS levels), modified Ferriman-Gallwey (mFG) score and the prevalence of acne and hirsutism decreased with increasing age, but also reported that visceral obesity and various metabolic disorders were significant concerns in aging women with PCOS.

In terms of menstrual cycles, the average age at menopause in women with PCOS is unclear. Anti-mullerian hormone (AMH) level may be a beneficial predictor of age-related ovulatory function among patients with PCOS with anovulatory cycles (25). One study, which used AMH as a predictive indicator, reported women's reproductive lifetime with PCOS lasted a mean two years longer than in normo-ovulatory individuals (26).

Long-term complications of aging women with PCOS

Obesity

The incidence of obesity, including visceral obesity, rises after menopause. This in turn encourages a number of metabolic disorders, including MS, diabetes and atherosclerosis (11). Visceral obesity is a frequently seen characteristic of PCOS, and one that exacerbates the severity of both reproductive and metabolic problems. Although several studies and meta-analyses showed a higher prevalence of overweight and obesity in women with PCOS than in women without PCOS, the data in aging women with PCOS are insufficient (9,27). Meun et al. (28) recently observed higher body mass index (BMI) values and increased waist circumferences in women with PCOS aged >45 years than in healthy controls. Wild et al. (29) reported significantly higher BMI and waist-to-hip ratio (WHR) values in a PCOS group than in a control group in a 31-year follow-up study. The Rotterdam study reported higher BMI and WHR in patients with PCOS than in age-matched controls (30). However, a 21-year follow-up study of patients with PCOS in the 61-79 age group (n=25) determined no differences in terms of BMI or WHR between patients and age-matched controls (n=68) (31). Echiburú et al. (32) investigated women with PCOS and healthy controls in three separate periods of reproductive life; women aged 18-34 years, 35-40 years and between 41-55 years. BMI and WHR values were higher among patients with PCOS in the early and late reproductive periods, but no difference was observed between the patients and controls in the perimenopausal period. Only homeostasis model assessment- β levels were lower in the late reproductive and perimenopausal periods in the patients with PCOS compared to early reproductive age (32). Overall most studies, but not all,

support the idea that women with PCOS at older ages persist in being more overweight/obese than healthy controls.

Metabolic syndrome

There is increased prevalence of MS associated with central obesity, insulin resistance, and HT in women after menopause. However, limited data are available concerning the prevalence of MS in women with PCOS during the perimenopausal period (9,10). Pinola et al. (20) reported a two- to five-fold higher prevalence of MS in women with PCOS compared with healthy controls, depending on age and phenotype. The highest prevalence was determined in hyperandrogenic women with PCOS towards the end of reproductive age (20). The Study of Women's Health Across the Nation (SWAN) study indicated no association between a history of HA or menstrual irregularity and impairment of metabolic condition after menopause (33). Meun et al. (28) did not observe significant difference in the prevalence of MS between women with PCOS and controls at the age of 50. Overall, women with PCOS experience a higher risk of MS during the reproductive period. However, with menopausal transition, the risk of MS becomes similar to that of women without PCOS.

Impaired glucose tolerance and type 2 diabetes mellitus

Studies have reported a greater prevalence of IGT and type 2 DM, independent of BMI, in women with PCOS (34). The SWAN study demonstrated a higher prevalence of IGT among women with PCOS with a mean age of 45.8 years compared to control subjects (25% vs 9.2%, respectively, $p < 0.001$) (33). Several long-term studies have identified PCOS as a risk factor for DM (35). Metabolic changes, such as insulin resistance, persist beyond menopause in women with PCOS, thus increasing their susceptibility to DM. Several studies have investigated the relationship between PCOS and DM in aging women (31,36,37). Wang et al. (38) reported a two-fold greater probability of DM incidence over a period of 18 years in women with PCOS in the CARDIA study. The probability of DM incidence was three times greater in normal-weight women with PCOS compared with weight matched healthy controls. The highest odds of diabetes [odds ratio (OR) 7.2, confidence interval (CI) 1.1-46.5] was detected among women with persistent PCOS fulfilling NIH criteria at baseline and during follow-up (38). A retrospective cohort study from the UK reported an age-dependent increase in the prevalence of DM, rising from 4.4% at ages 16-44, to 11.1% at 45-54 years, 15.7% at 55-64 years, and 45.4% at age >65. Although the OR of DM in PCOS was higher in all groups compared with age-matched women from the Health Survey for England, the

lack of adjustment for BMI in that study was described as a significant limitation (39). A prospective, follow-up study from Northern Finland reported a greater probability of DM at 46 years among women with presumed PCOS than in healthy control women (12.4% vs 4.3%; $p < 0.001$). Those authors reported that PCOS significantly enhanced the risk of DM in overweight/obese ($BMI \geq 25.0 \text{ kg/m}^2$) women with PCOS compared to weight matched healthy controls (OR: 2.45, 95% CI: 1.28-4.67), but not in normal-weight women (40). In a longitudinal study employing the Taiwan National Health Research Database, Lin et al. (41) observed that women with PCOS exhibited an increased risk of obstructive sleep apnea development in later life. They also found a greater prevalence of dyslipidemia (3.1% vs 2.4%, $p = 0.049$) and DM (2.4% vs 1.4%, $p = 0.001$) among individuals with PCOS compared to a control group (41). A higher prevalence of DM was also reported in the Rotterdam study among women with presumed PCOS compared to healthy control individuals (18.9% vs 7.0%, respectively, $p < 0.01$). However, again no adjustment was made for BMI or WHR when assessing risk of DM (30). Wild et al. (29) observed a higher prevalence of DM among women with PCOS than among age-matched controls (6.9% vs 3.0%, respectively, mean age 56.7 years), although that significant difference was no longer apparent following adjustment for BMI. Schmidt et al. (31) observed no significant difference in the prevalence of DM at 61-79 years of age, which may have been associated with the low numbers of participants and the relatively small PCOS population enrolled. Merz et al. (42) also determined no significantly greater prevalence of DM among postmenopausal women exhibiting clinical characteristics of PCOS in their long-term follow-up study. Finally, a cross-sectional study using the Dallas Heart study data, also observed no significant differences in terms of proportions of women with DM (36).

Limited evidence suggests that women with PCOS have an increased risk of DM in the perimenopausal period, and a higher risk of IGT during the reproductive period. The current recommendation is that all women with PCOS should be screened for DM at the initial visit, irrespective of age and BMI (12,23). Further research is now needed to illuminate this association after adjustment for risk factors including BMI and family history in older PCOS patients.

Dyslipidemia

Dyslipidemia is the most frequently seen metabolic disturbance in patients with PCOS, at rates as high as 70% according to National Cholesterol Education Program guidelines (12). Hypertriglyceridemia, low high-density lipoprotein (HDL)-cholesterol and high low-density lipoprotein (LDL)-cholesterol levels have been reported in both obese and lean women with

PCOS in previous studies (12,43,44). This atherogenic lipid profile derives from insulin resistance and HA, together with various genetic and environmental factors such as diet and lack of physical exercise (23). The most powerful evidence of an association between menopause and adverse cardiovascular risk alterations is this data showing pro-atherogenic changes occurring in the lipid profile (45). However, a small number of studies have investigated the prevalence of dyslipidemia in aging patients with PCOS (9,10). Wild et al. (43) reported lower HDL-cholesterol level, higher levels of TG, LDL-cholesterol and non-HDL cholesterol, independent of BMI, in women with PCOS. The CARDIA study showed a two-fold greater risk of incident dyslipidemia among women with PCOS during 18 years of follow-up (38). Pinola et al. (20) compared women with PCOS (normoandrogenic-NA or hyperandrogenic-HA) to healthy controls. These were classified under three age groups: <30, 30-39, and >39 years. In the HA-PCOS group women over 39 years-old exhibited higher LDL and triglyceride levels compared with the controls and higher LDL levels compared with the NA-PCOS population after adjustment for BMI. However, several studies showed no significant difference regarding dyslipidemia in aging women with PCOS (28,32,37,42). Meun et al. (30) reported lower HDL and higher triglyceride levels in women aged >55 years with PCOS. Schmidt et al. (31) observed that the levels of TG and LDL had increased, while HDL levels decreased, among women with PCOS during a 21-year follow-up period. Only higher TG levels persisted among postmenopausal women with PCOS compared to the controls (31). Hudecova et al. (46) reported significant differences regarding glucose, triglycerides, HDL-cholesterol, and blood pressure between patients with PCOS and healthy controls. However, following adjustment for BMI, postmenopausal status, and hormone use with multivariate linear regression analyses, only the difference in triglycerides was found to persist among Swedish women with previous histories of PCOS (46). In summary, dyslipidemia persists throughout life in women with PCOS, together with a heightened risk of dyslipidemia linked to obesity.

Hypertension

Several studies have reported a greater prevalence of HT in women with PCOS (37,47). One recent meta-analysis showed a greater prevalence of HT among patients with PCOS compared to control populations. However, this was observed only at reproductive age and not among menopausal women with histories of PCOS during the reproductive period (47). The Dallas Heart study showed higher incidences of BMI and HT among women with PCOS (mean age: 40 years) compared to control women with regular cycles. This was also found to persist at age-, BMI-, and ethnicity-matched analysis (36). Pinola et al. (20) reported significant increases in both

systolic blood pressure (SBP) and diastolic blood pressure in both PCOS populations compared with controls. In addition, higher rates of HT and higher BMI-adjusted SBP were found in hyperandrogenic women with PCOS aged over 39, although the mean values in both groups were within normal limits (20). Schmidt et al. (31) and Wild et al. (29) both observed higher prevalence of HT in women with PCOS, although other studies have reported no significant differences in the prevalence of HT between aging women with PCOS and the general population (30,38,42).

The risk of HT is generally higher among women with PCOS. However, further research is now needed to establish the risk of HT in aging women with PCOS beyond menopause.

Cardiovascular disease and risk factors

The menopausal transition is characterized by significant alterations in cardiovascular risk factors. These are associated with both chronological and ovarian aging. High circulating androgen levels have been linked to an unfavorable cardiovascular risk profile and a greater prevalence of subclinical atherosclerosis among women of postmenopausal age (10,48). Although many studies have shown a greater incidence of cardiometabolic risk factors among women with PCOS, there has been little evaluation of this association in older women with PCOS (10). Recent guidelines recommend that adolescents and women with PCOS be screened for CVD risk factors, such as a family history of early CVD, smoking, IGT/DM, HT, dyslipidemia, and abdominal adiposity (23,49). In addition to these familiar cardiovascular risk factors, a number of studies have also associated PCOS with an increased carotid artery intima media thickness (CIMT), decreased arterial flow-mediated dilation, and coronary artery calcium (CAC) elevation (38,50,51). In a study of 125 women with PCOS and 142 healthy controls, Talbott et al. (51) observed greater CIMT in patients with PCOS (0.78 mm) compared to control women aged 45 or more (0.70 mm). These authors also reported that the difference remained significant, even after adjustment for BMI (51). On the 20th year of the CARDIA study, higher mean internal CIMT and bulb mean CIMT values were observed among women with PCOS evaluated at 45 years of age than in healthy controls. These patients also exhibited a 2.7-fold greater probability of elevated CAC (aOR: 2.7, 95% CI 1.31-5.60) compared with the healthy controls (38). In contrast, research from the Dallas Heart study recently reported a similar prevalence of CAC scores >10 among women with PCOS who had both oligomenorrhea and HA (n=55), and women with PCOS according to the Rotterdam criteria (n=144) and healthy controls with normal ovulation (n=170), despite a higher prevalence of CVD risk factors among women with PCOS (36). No association was observed between presumed

PCOS and either greater CIMT or peripheral artery disease in the Rotterdam study (30). Meun et al. (28) recently investigated the cardiometabolic characteristics and prevalence of CVD in middle-aged patients with PCOS (mean age: 50.5 years) compared with age-matched controls. No evidence was found suggesting an increased 10-year cardiovascular risk or more serious atherosclerosis compared with control women from the general population (28).

Despite evidence supporting the idea of a greater risk of subclinical atherosclerosis in women with PCOS, the results of studies investigating the prevalence of CVD events are controversial, especially in post-menopausal women. A retrospective cohort analysis from the United Kingdom that spanned 20 years reported high incidences and age-specific prevalence of DM, myocardial infarction (MI) and angina among women with PCOS, with more than 25% of women with MI or angina being over 65 (39). However, no relationship was determined in the Rotterdam study between androgen elevation and incidence of stroke, coronary heart disease (CHD), or CVD (30). Another follow-up study of women with PCOS reported that CVD risk markers persisted into the postmenopausal period with no heightened incidence of stroke, CVD or mortality (31). No association with CHD or mortality was observed in a small cohort of postmenopausal PCOS patients exhibiting a trend toward more prevalent CHD, with multi (two or three) vessel disease being determined in 42% patients compared with 27% of women without clinical characteristics of PCOS (42). However, great caution must be employed when interpreting the findings of all such studies, particularly in the light of methodological and reporting limitations, incomplete diagnosis of PCOS, and the small sample sizes involved. Iftikhar et al. (52) observed no increase in CV events, including MI, coronary artery bypass graft surgery, death due to CV disease, and stroke, over 20-year follow-up. Wild et al. (29) reported that while a history of CHD was not significantly more frequent in women with PCOS, the crude OR for stroke was 2.8 (1.1±7.1). The incidence of stroke may be due to the longer follow-up period and older age. A recent study from the National Registry in Denmark reported a greater risk of CVD (HR: 1.3, 95% CI 1.2-1.4) in premenopausal patients with PCOS following adjustment for confounders, including obesity and DM. Obesity, DM, infertility, and previous use of oral contraceptive were associated with a heightened risk of development of CVD in these patients (53).

Studies and guidelines state that cardiometabolic risk factors are more prevalent among women with PCOS. Lifestyle management and modification are particularly recommended for primary CVD prevention, targeting dyslipidemia, and glucose abnormalities. Metformin and treatments for dyslipidemia should be added if necessary (44,49).

Cancer

Women with PCOS are exposed to risk factors, including null-parity, obesity, and prolonged unopposed estrogen, that are associated with EC. Barry et al. (54), reported a significantly greater risk of EC (OR: 2.79; 95% CI, 1.31-5.95, $p=0.008$) among women with PCOS, but that no significant change occurred in the risk of ovarian and breast cancers. However, once studies involving subjects aged over 54 years had been removed from the results, the risk for women with PCOS increased for EC and significantly for ovarian cancer, although no significant risk was observed for breast cancer (54). In addition, a cohort of 786 women with PCOS (mean age: 56.7 years) were followed-up for a mean 31 years (range: 15-57) following diagnosis of PCOS. The prevalence of EC was higher among women with PCOS than in the control subjects (2.2% vs 0.4%; $p=0.001$) (55). Based on The Danish National Patient Register data, Gottschau et al. (56) calculated an overall four-fold increased risk of EC, but found no relationship between PCOS and breast or ovarian cancer. In summary, although the small numbers of events involved represent a limitation in these studies, health professionals and women with PCOS should nevertheless be aware of a two- to six-fold increased risk of EC.

Conclusion

PCOS is a reproductive and metabolic disorder associated with a number of long-term health risks such as obesity, IGT, T2DM, HT, dyslipidemia, MS, cardiovascular risk factors, and EC during reproductive age, especially in patients possessing classic phenotypes. However, the question of whether the presence of PCOS results in a significant increase in such morbidity and mortality in older women with PCOS is still controversial. Although these cardiometabolic risk factors are more common among women with PCOS, currently there is no strong evidence for increased cardiovascular morbidity and mortality in aging women with PCOS.

An established, long-term history of OA and HA during the reproductive years in the peri-postmenopausal period may suggest a presumptive diagnosis of PCOS. The majority of studies concerning this topic have a number of limitations, including self-report diagnosis, being retrospective or cross-sectional in character, small sample sizes, inappropriate diagnostic criteria for PCOS without defining phenotypes, and limited follow-up. Extensive prospective cohort studies in which healthy controls in addition to patients with defined PCOS phenotypes are observed and monitored from the early reproductive period into the late postmenopausal period should now be performed in order to clarify morbidities and mortality in older women with PCOS.

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