Polycystic Ovary Syndrome-Related Risks in Postmenopausal Women

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16.1 Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder of reproductive life, with an estimated prevalence of 6–20%, depending on the criteria used [1]. Three different definitions have been used so far: (a) National Institutes of Health (NIH) (1990), which requires the presence of both hyperandrogenism and oligo- or anovulation; (b) Rotterdam criteria (2003), which requires two out of the following three, oligo- or anovulation, hyperandrogenism (either clinical or biochemical), and polycystic ovarian morphology (PCOM); and (c) Androgen Excess PCOS Society (AEPCOS), which requires the coexistence of hyperandrogenism (either clinical or biochemical), as a sine qua non for PCOS diagnosis, and either PCOM on ultrasound or clinical anovulation [1]. According to NIH criteria, the prevalence of PCOS is estimated at 8.7%, rising to 17.8% with the Rotterdam criteria and approaching 12% with the AEPCOS definition [2]. These criteria can be applied only in premenopausal women, after excluding other causes of androgen

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excess [1]. In postmenopausal women, there is no uniform definition of PCOS. A potential, but precarious, diagnosis can be indirectly set in cases of menstrual irregularity (oligo- or amenorrhea) during the reproductive ages and current clinical and/or biochemical hyperandrogenism [3, 4].

PCOS has been associated with metabolic disorders, with insulin resistance (IR) being the central pathogenetic component. These disorders include impaired glucose metabolism [predisposing to type 2 diabetes mellitus (T2DM)], dyslipidaemia, hypertension and central adiposity [1, 3]. Whether these PCOS-related cardiometabolic risk factors are also translated into an increased cardiovascular disease (CVD) risk in postmenopausal life remains to be established.

The purpose of this chapter is to present current data on the association between PCOS and the risk of co-morbidities, such as T2DM, hypertension, CVD and cancer, in postmenopausal women.

16.2 Diabetes Mellitus in Postmenopausal Women with PCOS

In general, PCOS is associated with increased IR and concomitant higher risk of impaired glucose tolerance (IGT) or T2DM. The prevalence of IR in lean and obese PCOS women is estimated at 30% and 70%, respectively [5]. Only obese women with PCOS are prone to exacerbating IR and developing T2DM during the ageing process. Thus, not all women with PCOS should be considered as "high risk" of T2DM, since weight loss may ameliorate T2DM risk [6]. Except for body mass index (BMI), the risk of developing IGT or T2DM is dependent on the ethnicity (higher in Hispanic than non-Hispanic PCOS women), the PCOS phenotype (type 1, including all three Rotterdam criteria, presents the highest IR and type 4, with PCO morphology and hyperandrogenism, the lowest), testosterone (positive relation with IR) and sex hormone-binding globulin (SHBG) concentrations (negative relation with IR) [1].

A meta-analysis of 35 studies, published in 2010, showed that women with PCOS are at a 2.5-fold risk of IGT [OR 2.48, 95% confidence interval (CI) 1.63–3.77] and more than fourfold risk of T2DM (OR 4.43, 95% CI 4.06–4.82). These OR remained significant after adjustment for BMI (OR 2.54, 95% CI 1.44–4.47 for IGT and 4.00, 95% CI 1.97–8.10) for T2DM [7]. However, in this meta-analysis only two studies were conducted in premenopausal women [8, 9]. The first [8] included 28 perimenopausal women with PCOS (mean age 51.9 years) and showed a higher risk of T2DM compared with 752 non-PCOS controls (32% versus 8%, $p < 0.001$), as defined by increased fasting plasma glucose (FPG) concentrations ($\geq$7 mmol/L). Except for the small sample size, another limitation was the low proportion of postmenopausal women (35.7%) [8]. The second study [9] was conducted exclusively in postmenopausal women with PCOS and showed a higher risk of T2DM; nevertheless, it was withdrawn due to inability of the authors to replicate the original results.

In general, few studies have assessed T2DM risk in postmenopausal women. One retrospective study included 2301 women with PCOS, defined by the NIH and Rotterdam criteria. For the age groups 45–54, 55–64 and >65 years, the ORs for T2DM were 3.75 (95% CI 2.59–5.43), 2.89 (95% CI 1.57–5.34) and 7.09 (2.15–23.35), respectively, compared with the general female population. The overall OR was 2.02 (95% CI 1.71–2.38). This increased T2DM risk was affected by a history of hypertension, older age, obesity and South Asian ethnicity [10]. However, a prospective cohort study in 295 postmenopausal women with PCOS (defined as premenopausal menstrual irregularity and postmenopausal biochemical hyperandrogenism) failed to show an independent effect of the history of PCOS on the development of T2DM in later life, after a median follow-up of 9.3 years [11]. In a cross-sectional study, the prevalence of T2DM in postmenopausal women with PCOS ($n = 106$, defined by a history of both cycle irregularities and biochemical hyperandrogenism) was higher than in women without PCOS ($n = 171$, 20% versus 7%, $p < 0.01$) [12].

The effect of menopause per se on the deregulation of glucose metabolism during the menopausal transition should be considered when assessing the impact of PCOS history on T2DM risk. This is mainly attributed to the increased abdominal obesity and concomitant insulin resistance as well as to a defect in insulin secretion, as a result of oestrogen depletion [13]. It is not clear if these pathogenetic mechanisms are entirely independent of the ageing process [13]. Another confounding factor could be the past use of oral contraceptives (OC), anti-androgens or insulin sensitizers that may affect evolution to T2DM following menopause in women with PCOS. Of note, a recent meta-analysis showed that OC use does not affect FPG (irrespective of the regimen) or IR indices, such as the homeostasis model assessment of insulin resistance (HOMA-IR) [14]. Concomitant use of anti-androgens, such as cyproterone acetate, may increase HOMA-IR and abolish possible beneficial or neutral effects of OC [15].

16.3 Arterial Hypertension in Postmenopausal Women with PCOS

Most studies show a higher prevalence of (mainly systolic) hypertension in women with PCOS, at least in their later post-reproductive life, compared with the general population [1]. The exact pathogenetic mechanisms are not fully elucidated, since both BMI and IR may play a role. Independent factors have been suggested, such as activation of the renin-angiotensin system by testosterone; testosterone seems to increase plasma renin concentrations and angiotensin-converting enzyme activity [16], although this hypothesis has not been confirmed [17].

In general, data regarding the effect of PCOS on the risk of developing hypertension in postmenopausal women are inconclusive, mainly due to the different study design, the small number of patients and the various definitions used. A prospective study (including 35 women with PCOS and 68 age-matched controls, mean

age 70.4 and 70.7 years, respectively, with 21 years of follow-up) showed a higher prevalence of hypertension in PCOS (histologically verified Stein-Leventhal syndrome at wedge resection) compared with controls (69% versus 41%, $p = 0.008$) [18]. However, another prospective cohort study in 295 postmenopausal women failed to show an independent effect of PCOS on the development of hypertension in later life, after a median follow-up of 9.3 years [11].

A cross-sectional study included 286 asymptomatic postmenopausal women (43 with PCOS) and showed that PCOS was characterised by higher systolic and diastolic blood pressure (BP) compared with controls. However, BP did not reach hypertensive levels in either group [systolic BP, 127.0 ± 20.5 versus 118.3 ± 15.3 mmHg, ($p = 0.001$); diastolic BP, 78.7 ± 11.8 versus 74.4 ± 10.2 mmHg ($p = 0.014$)] [19]. However, a cross-sectional study did not find any difference in either systolic or diastolic BP between perimenopausal women with ($n = 35$) or without PCOS ($n = 752$). Of note, only ten PCOS women were postmenopausal [8].

Some confounding factors should be taken into consideration when evaluating the risk of hypertension in postmenopausal women with a diagnosis of PCOS. Transition to menopause per se may increase the risk of arterial hypertension, irrespective of BMI [20, 21]. The decline in oestrogen concentrations during menopause and the decline in oestrogen/androgen ratio increase the production of vasoconstrictive factors, such as endothelin and angiotensinogen, as well as the sympathetic activity [22]. The effect of OC use during the reproductive years on the development of hypertension in later life is not known, although current data do not indicate such a detrimental effect [14].

16.4 Dyslipidaemia in Postmenopausal Women with PCOS

PCOS has been associated with an atherogenic lipid profile in 70% of the cases, including increased low-density lipoprotein cholesterol (LDL-c), very-low-density lipoprotein cholesterol (VLDL-c), triglyceride (TG) and free fatty acid concentrations, as well as decreased high-density lipoprotein cholesterol (HDL-c) concentrations, mainly HDL2-c, due to reduced apolipoprotein A-I (apoA-I). The quality of LDL particles is also affected in PCOS, since it is characterised by the predominance of small and dense LDL particles and higher concentrations of oxidised LDL-c. These disorders of lipid metabolism are independent of BMI but may be aggravated by obesity and IR [1]. On the other hand, menopause per se is also associated with these alterations [23, 24], as well as a potential increase in lipoprotein (a) [Lp(a)] concentrations [25], further augmenting CVD risk.

It can be concluded that the effect of PCOS on lipid profile in postmenopausal women cannot be precisely estimated, taking into account the heterogeneity in PCOS definition and study design, as well as the use of hypolipidaemic drugs and OC in the past [26]. Prospective cohort and cross-sectional studies have shown either a null effect of PCOS history on lipid profile [8, 11] or an increase in TG and a decrease in HDL-c concentrations during postmenopausal years [12, 18, 19]. No difference has been identified in any lipid parameters in the retrospective studies [27].

16.5 Cardiovascular Risk in Postmenopausal Women with PCOS

Data from premenopausal women indicate that PCOS confers a potentially higher CVD risk in these patients, considering the higher prevalence of traditional CVD risk factors and CVD surrogate markers, such as arterial stiffness and carotid intima-media thickness (cIMT), compared with their age-matched controls. However, whether postmenopausal women with PCOS are indeed at a higher risk of CVD events compared with postmenopausal women without a history of PCOS has not been yet established. Many factors compromise the exact estimation of this risk. First, most data derive from retrospective cohort and case-control studies. Second, the definition of PCOS in postmenopausal women is quite obscure, based mostly on the history of irregular menses during the reproductive age and the presence of biochemical or clinical hyperandrogenism. Third, the ultrasound criterion of PCOM cannot be implicated in postmenopausal women. Fourth, some of these women have been treated with agents that may have affected the metabolic profile with unknown consequences on their CVD risk, such as OC and/or anti-androgens. Fifth, some clinical features in postmenopausal women, such as menstrual irregularities, may be attributed to other surgical or anatomical causes than PCOS. This limitation is further expanded considering that the pattern of menstruation due to PCOS during the reproductive ages usually improves during the last years before the menopausal transition. Sixth, the most crucial parameter compromising an independent effect of PCOS on CVD risk is the age- and menopause-associated deterioration of the metabolic profile (including body fat redistribution leading to increased central adiposity [28], dyslipidaemia [23, 24], deregulation of glucose metabolism [29, 30], arterial hypertension [30]), which confers a well-established CVD risk.

Three meta-analyses have been conducted on the concept of assessing CVD risk in women with PCOS. Despite the heterogeneity in study design and quality, as well as PCOS definition, these meta-analyses showed a higher CVD risk in PCOS than in women without PCOS. However, this risk was found to be lower than the one predicted by the accumulation of CVD risk factors during the premenopausal ages. The first one [31], which included three retrospective and two prospective studies, showed a twofold increased risk for the composite outcome of coronary heart disease (CHD) events and stroke [pooled relative risk (RR): 2.02, 95% CI 1.47–2.76]. After using BMI-adjusted risk data, the RR remained significant (1.55, 95% CI 1.27–1.89) [31].

The second meta-analysis [32] assessed the risk for nonfatal CHD events and stroke between women with and without PCOS and showed no significant results (OR: 1.61, 95% CI 0.82–3.15 and 1.63, 95% CI 0.96–2.78, respectively). When the analysis was confined to women older than 45 years, the risk for nonfatal stroke was increased in women with PCOS (OR: 1.94, 95% CI 1.19–3.17), whereas this was not true for CHD (OR: 1.70, 95% CI 0.92–3.11). This difference was not shown, when the analysis was restricted to studies ($n = 3$) with similar BMI values between women with and without PCOS.

The third meta-analysis included data from five case-control and five cohort studies. It also showed an increased risk of CVD in women with PCOS compared with controls (OR: 1.30, 95% CI 1.09–1.56), especially for CHD (OR: 1.44, 95% CI 1.13–1.84). In a subgroup analysis, the risk remained increased only for case-control and prospective cohort studies (OR: 1.79, 95% CI 1.16–2.77 and 1.20, 95% CI 1.06–1.37, respectively), but not for retrospective studies [33].

The effect of PCOS on CVD risk cannot be safely extrapolated to postmenopausal women, mainly for two reasons. First, the proportion of postmenopausal women in the study samples was relatively small or not reported [8, 27, 34]. Second, the diagnosis of PCOS was not based on NIH or Rotterdam criteria in most studies, but on menstrual irregularity [35, 36]. In some studies, the number of women with PCOS was very small to draw safe conclusions for CVD risk [8, 18, 37]. A study that overcame most of these methodological restraints [10] included 2301 women with PCOS, using the NIH or Rotterdam criteria. For age groups of 45–54, 55–64 and >65 years, the OR for myocardial infarction (MI) were 10.63 (95% CI 4.93–22.90), 9.27 (95% CI 3.73–23.03) and 12.88 (95% CI 3.41–48.00), respectively. The OR for the composite outcome of MI, angina, heart failure, cerebrovascular death and CVD death was increased for these age groups (2.95, 95% 1.81–4.83; 3.09, 95% CI 1.64–5.84; and 6.31, 95% CI 1.84–21.56, respectively), providing evidence for an association of PCOS with CHD risk in postmenopausal life. In a logistic regression analysis, this risk was affected by age, history of hypertension and smoking, but not by BMI and T2DM [10].

A cross-sectional study conducted in 390 postmenopausal women with clinical features of PCOS showed a higher prevalence of angiographic coronary artery disease (CAD) compared with women without PCOS. Furthermore, the cumulative 5-year CVD event-free survival was lower (78.9% versus 88.7%) [9]. However, this study was withdrawn because of the inability of the authors to replicate their results [11]. Eight years later, the same group published the results from their prospective cohort (n = 295), after a median follow-up time of 9.3 years. PCOS was defined as premenopausal menstrual irregularities in combination with postmenopausal biochemical hyperandrogenism. The study failed to show an effect of the history of PCOS on the development of CAD, CVD and all-cause mortality [11].

The risk for CVD in women with PCOS seems to be elevated even from the premenopausal ages. A Danish register-based study (n = 18,112, median age 29 years, range 23–35 years, follow-up time 11.1 years) showed that women with PCOS were at an increased risk of CVD [hazard ratio (HR): 1.7, 95% CI 1.7–1.8] compared with their age-matched controls. The total CVD event rate was 22.6/1000 patient-years and a median age at CVD diagnosis of 35 (range 28–42) years. This risk was affected by obesity, T2DM, history of infertility and/or previous OC use [38]. Hyperandrogenism did not seem to affect CVD risk in postmenopausal women with PCOS [12, 39].

Premenopausal women with PCOS have a higher prevalence of subclinical atherosclerosis compared to controls as it is evident by surrogate markers for CVD, such as arterial stiffness [assessed by means of pulse wave velocity (PWV)], arterial structure (evaluated by means of cIMT) and coronary artery atherosclerosis (CAC)

[1, 40]. This association is confirmed by two meta-analyses [41, 42]. In postmenopausal women, very few studies exist. In one representative study of asymptomatic postmenopausal women (n = 286), PCOS diagnosis was independently associated with increased arterial stiffness, as assessed by PWV. No difference in cIMT was observed between postmenopausal women with and without PCOS [19].

The Coronary Artery Risk Development in Young Adults (CARDIA) study assessed a mixed population of pre- and postmenopausal women for CAC (n = 982) and cIMT (n = 988). Fifty-five of those (mean age 45.4 years, 12.7% postmenopausal) were defined as PCOS, when both menstrual irregularities and hyperandrogenism existed. The prevalence of CAC was higher in PCOS compared with healthy controls or those women with isolated irregular menses or isolated hyperandrogenism, yielding an OR of 2.69 (95% CI 1.37–5.25), independently of CVD risk factors, such as obesity, menopausal status, hypertension, smoking, HOMA-IR and TG. Similar OR were observed for PCOS with regard to internal cIMT (OR: 2.00, 95% CI 1.07–3.75) [43]. However, others found no association between PCOS phenotype and indices of subclinical or clinical CVD in postmenopausal women [12].

16.6 Cancer Risk in Postmenopausal Women with PCOS

PCOS is characterised by chronic hyperoestrogenaemia, unopposed by progesterone, due to anovulation, a state associated with increased risk of some types of cancer, such as breast, endometrial and ovarian cancer. In a meta-analysis (11 studies, 919 women with and 72,054 without PCOS), no increased risk was found for breast cancer (OR: 0.95, 95% CI 0.64–1.39), a finding that remained non-significant after excluding studies conducted in women older than 54 years (OR: 0.78, 95% CI 0.46–1.32) [44]. Other systematic reviews and meta-analyses were confirmatory [45, 46]. However, PCOS has been associated with a high risk of endometrial cancer (OR: 2.79, 95% CI 1.31–5.95), which was further increased when studies including women >54 years were excluded (OR: 4.05, 95% CI 2.42–6.76) [44]. However, these findings were not adjusted for BMI. Studies that reported effect estimates adjusted for BMI provided inconsistent results with either increased or attenuated ORs or lack of significance [45].

The association between PCOS and ovarian cancer has been attributed to the chronic androgen exposure and the presence of androgen receptors in normal ovarian cells [45]. The aforementioned meta-analysis [44] did not show any association between PCOS and ovarian cancer risk (OR: 1.41, 95% CI 0.93–2.15), which reached significance after excluding studies in women aged >54 years (OR: 2.52, 95% CI 1.08–5.89). Perhaps, there is an association of PCOS with an increased risk of only the serous borderline subtype of ovarian cancer [45]. This finding was not supported by a recent study for any ovarian cancer both for women with self-reported PCOS and those with a history of menstrual cycle length >35 days [47].

The potential effect of obesity and long-term use of OC [48] should be taken into consideration when evaluating the link between PCOS and cancer. In a nationwide study, the OR for cancer ranged from 1.09 (95% CI, 0.96–1.23) with <1 year of OC use to 1.38 (95% CI, 1.26–1.51) with >10 years of use [49].

16.7 Conclusions: Future Perspectives

PCOS is associated with an increased prevalence of CVD risk factors, such as deregulation of glucose metabolism, dyslipidaemia and arterial hypertension, predisposing to the development of subclinical atherosclerosis and CVD. Despite the clustering of these risk factors, an association between PCOS and CVD has not been established in the post-reproductive life, at least to the extent that would be expected. Many reasons contribute to this phenomenon, such as the heterogeneity of both PCOS and CVD definitions in postmenopausal women, study design, small sample size, amelioration of menstrual pattern with ageing and insufficient follow-up. Well-designed, high-quality prospective studies are needed to establish whether the history of PCOS confers an independent CVD risk in postmenopausal women, irrespective of obesity, ageing and menopause per se. Finally, there is no evidence of an association between PCOS and breast or ovarian cancer, as a consequence of prolonged unopposed oestrogen and androgen stimulation. However, this is not the case for endometrial cancer, although an independent effect of obesity should be considered.

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