

## REVIEW

# Cardiometabolic risk in polycystic ovary syndrome

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## Abstract

Polycystic ovary syndrome (PCOS) is a common disorder in women of reproductive age. Besides hyperandrogenism, oligomenorrhea and fertility issues, it is associated with a high prevalence of metabolic disorders and cardiovascular risk factors. Several genetic polymorphisms have been identified for possible associations with cardiometabolic derangements in PCOS. Different PCOS phenotypes differ significantly in their cardiometabolic risk, which worsens with severity of androgen excess. Due to methodological difficulties, longer time-scale data about cardiovascular morbidity and mortality in PCOS and about possible beneficial effects of different treatment interventions is missing leaving many issues regarding cardiovascular risk unresolved.

## Key Words

- ▶ PCOS
- ▶ cardiovascular risk
- ▶ cardiometabolic risk
- ▶ hyperandrogenism
- ▶ obesity

*Endocrine Connections*  
(2018) **7**, R238–R251

## Introduction

Polycystic ovary syndrome (PCOS) is a common disorder in women of reproductive age, with a prevalence 5–16% under different diagnostic criteria and across several ethnic groups, with exact pathogenesis still unclear (1, 2, 3). General agreement exists now among the community of endocrinologists and gynecologists that the diagnosis of PCOS should be based on the Rotterdam criteria, which include two of the following three features: oligo-/amenorrhea, hyperandrogenism (clinical or biochemical) and polycystic ovaries on ultrasound, after exclusion of other endocrinopathies (4). These criteria have broadened the spectrum of PCOS phenotypes in contrast to those defined previously by the 1990 National Institutes of Health (NIH) criteria that required both oligo-/anovulation and clinical or biochemical hyperandrogenism for the diagnosis of PCOS (5). The Rotterdam diagnostic criteria have led to the generation of four distinct phenotypic subgroups: the 'PHO' subgroup with all three diagnostic features present; the 'HO' subgroup with hyperandrogenism and oligo-/amenorrhea, the 'PH' subgroup with polycystic

ovaries on ultrasound and hyperandrogenism and the 'PO' subgroup with polycystic ovaries on ultrasound and oligo-/amenorrhea.

Besides the clinical features of hyperandrogenism (hirsutism, acne, male-type baldness), oligo-/amenorrhea and impaired fertility, PCOS patients are often insulin resistant, obese and have metabolic syndrome, with arterial hypertension, dyslipidemia, impaired glucose tolerance or frank type 2 diabetes, low-grade inflammation and increased pro-thrombotic state (2). This high prevalence of cardiovascular risk factors in PCOS is assumed to be associated with accelerated cardiovascular disease. However, clear data from large end point trials about cardiovascular morbidity and mortality in PCOS is currently lacking, although there are plenty of data on early occurrence of subclinical, potentially reversible atherosclerosis in women with PCOS (6). The aim of this article is to explore and review current evidence that associates PCOS with cardiometabolic abnormalities and possibly an increased risk of cardiovascular disease.

## Insulin resistance, metabolic syndrome, obesity and sleep disturbances in PCOS and cardiovascular risk

### Insulin resistance

In PCOS patients, basal insulin secretion rates are increased, although insulin secretory responses to a glucose load are generally inadequate in comparison to healthy subjects (7, 8). At a tissue level, insulin resistance is present in the liver, adipose tissue and muscles of these patients. The PCOS-associated insulin resistance is selective, affecting metabolic, but not mitogenic, signaling pathways, which might explain the paradox of persistent reproductive actions of insulin in the face of systemic insulin resistance (8). In approx. 40% of women with PCOS defined by NIH criteria, impaired glucose tolerance or type 2 diabetes mellitus as consequences of insulin resistance develop by their fourth decade of life, with age and weight gain having an adverse effect on glycemic control (9, 10, 11, 12, 13, 14). Moreover, a study basing PCOS diagnosis on Rotterdam criteria reported insulin resistance in 71.4% of included subjects (15). However, insulin resistance frequency significantly differed among phenotypes, being 80.4% in the 'classic NIH phenotype' group (including the above mentioned 'PHO' and 'HO' phenotypes), 65.0% in the ovulatory group (the above mentioned 'PH' phenotype) and 38.1% in the normoandrogenemic group (the above mentioned 'PO'), respectively. The classic phenotype and, to a lesser extent, the ovulatory phenotype were independently associated with insulin resistance, whereas the normoandrogenic phenotype was not. This was confirmed by another study which showed that the number of PCOS patients with homeostatic model assessment insulin resistance (HOMA-IR) index >3.8 was significantly higher in androgenic phenotypes in comparison to other phenotypes (16).

### Metabolic syndrome

Insulin resistance is a central mechanism linking together all components of the metabolic syndrome, defined by the presence of hyperglycemia (fasting glucose levels 5.6 mmol/L or above), central obesity (increased waist circumference by population and country specific definitions), low high-density lipoprotein (HDL) cholesterol level (<1.29 mmol/L in women), high total triglyceride level (1.7 mmol/L or above) and elevated arterial blood pressure (130/85 mmHg or above) (17, 18). The prevalence of metabolic syndrome is significantly higher in PCOS population as compared to BMI-matched

controls. In the United States, it is estimated to be two to three times higher than that of age-matched controls (19, 20, 21). However, its prevalence was found to be lower in countries with lower prevalence of obesity such as Spain or Italy, ranging between 8 and 25% in women with classic PCOS (22, 23). Regarding the Rotterdam criteria of PCOS, metabolic syndrome prevalence was significantly higher in phenotypes 'PHO' and 'HO' (29.6% and 34.5%, respectively) compared with the other phenotypes (10.0% in 'PH' and 8.3% in 'PO') (16).

Many conditions, mainly components of the metabolic syndrome, have been recognized as risk factors for cardiovascular disease, such as impaired glucose tolerance, type 2 diabetes mellitus, dyslipidemia, abdominal obesity and hypertension (24).

### Obesity

A large proportion of women with PCOS are overweight, obese or centrally obese, with data regarding prevalence again varying across different populations (25, 26). Patients with PCOS have increased proportion of central to peripheral fat ratio when compared to controls (27, 28, 29). Obesity, particularly of visceral origin, plays a crucial role in both development and maintenance of PCOS (30, 31) and significantly influences the severity of metabolic and cardiovascular risk profile (32, 33). In PCOS, obesity is a well-documented risk factor for abnormal glucose tolerance with increased rates of impaired glucose tolerance and type 2 diabetes, metabolic syndrome and dyslipidemia (19, 24, 34).

A recent review of studies on obesity in PCOS showed that overweight and obese women with PCOS had increased fasting glucose, fasting insulin, HOMA-IR index and worsened lipid profile (35). Obesity significantly worsened all metabolic and reproductive measures except for hirsutism when compared to normal women with PCOS. Central obesity was associated with higher fasting insulin levels. This study also reported that in overweight and obese PCOS women, the fasting lipid profile worsens.

It still remains an open issue whether lean women with PCOS are at increased cardiovascular risk (24). Lean women with PCOS demonstrate intrinsic abnormalities in body fat distribution and insulin resistance (36). Even in normal-weight girls (age  $15.9 \pm 1.8$  years, BMI  $22.7 \pm 2.3$ ) with PCOS, decreased peripheral insulin sensitivity and muscle mitochondrial dysfunction, abnormal glucose disposal, relative postprandial hyperinsulinemia and increased hepatic fat content compared to normal-weight controls were reported (37).

PCOS patients often have lower sex-hormone-binding globulin (SHBG) levels, which could be further exacerbated with obesity (38). SHBG has been shown to be positively associated with HDL and physical fitness and negatively associated with obesity, central fat distribution, triglycerides, insulin resistance and diabetes (39).

### Sleep disturbances and disorders in PCOS

There is also a growing body of evidence suggesting that sleep disturbances including obstructive sleep apnea (OSA) and excessive daytime sleepiness can be added to the list of cardiometabolic risk factors in PCOS with link between the two being complex and possibly bidirectional (40, 41). OSA is a relatively common and chronic sleep disorder characterized by recurrent complete (apnea) or partial (hypopnea) upper airway obstruction during sleep leading to intermittent hypoxia, cortical microarousals, sleep fragmentation, increased sympathetic neural activity, hypothalamus–pituitary–adrenal axis dysregulation, altered cytokine release and oxidative stress (42). There is also strong evidence suggesting that OSA contributes to the development of hypertension, cardiovascular disease and abnormalities in glucose metabolism (43, 44, 45). A recent meta-analysis suggests that risk of OSA is increased in adult women with PCOS. It seems that central obesity, hyperandrogenemia and insulin resistance, either alone or in concert, could be implicated in the development of OSA in women with PCOS (40). However, at present, there is scarce evidence about possible cardiometabolic improvement of OSA treatment in PCOS, although continuous positive airway pressure (CPAP) has been shown to be a promising treatment for OSA in young obese women with PCOS, with improvements in insulin sensitivity, daytime diastolic blood pressure and cardiac sympathovagal balance after 8 weeks of treatment (46). More interventional trials in PCOS patients are lacking. In the general OSA subpopulation (mostly men), there is now evidence from systematic reviews with meta-analyses that CPAP reduces blood pressure and endothelial dysfunction (47, 48, 49). Systematic reviews with meta-analysis have also indicated that insulin resistance can be improved with CPAP use in OSA patients, thereby possibly reducing the risk of developing type 2 diabetes in non-diabetic and pre-diabetic individuals (50).

Therefore, it would seem prudent to screen PCOS patients for clinical features and symptoms associated with OSA and refer the ones at risk for further evaluation with overnight polysomnography and treatment, although the new international PCOS guidelines that are in preparation do not recommend these steps.

### Other/non-classical cardiovascular risk factors in PCOS

PCOS is also associated with changes in circulating factors of coagulation and fibrinolysis, such as increased levels of factor VIIc, von-Willebrand's factor, thrombomodulin, D-dimer, antithrombin III and fibrinogen (51, 52). Thrombin activatable fibrinolysis inhibitor levels were reported to be higher in PCOS women (in comparison to age- and BMI-matched healthy controls) possibly contributing to hypofibrinolytic state and accelerated atherosclerosis (53).

A study evaluating oxidative stress and leukocyte adhesion (both being implicated in the etiology of chronic low-grade inflammation and early cardiovascular risk) in PCOS, an increase in the rate of reactive oxygen species and myeloperoxidase levels was reported, particularly in patients with insulin resistance. Moreover, it was shown that inflammation in PCOS induces leukocyte–endothelium interactions and a simultaneous increase in interleukin-6, tumor necrosis factor (TNF) alpha, E-selectin, adhesion molecules such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, which are all aggravated in the presence of insulin resistance (54).

Moreover, a very recent large retrospective longitudinal cohort study in the United Kingdom evaluating nonalcoholic fatty liver disease (NAFLD) rates in 63,120 women with PCOS and 121,064 age-, BMI- and location-matched control women found that women with PCOS have an increased rate of NAFLD (HR=2.23, 95% CI 1.86±2.66,  $P<0.001$ ). The incidence of NAFLD increased with increasing androgen and decreasing SHBG levels (87). NAFLD is associated with increased mortality due to an increased risk from cardiometabolic complications and death from liver failure and hepatocellular carcinoma (55, 56). Similar findings in PCOS women were also reported previously by smaller studies and systematic reviews (57, 58, 59).

In PCOS, serum advanced glycation end products (AGEs) are distinctly elevated compared with women having the isolated characteristics of the syndrome (60). It has been suggested that chronic inflammation and increased oxidative stress may be a link between the mechanisms of AGEs action and the metabolic and reproductive consequences of PCOS. High dietary AGEs intake promotes deteriorating biological effects in women with PCOS, whereas AGEs restriction seems to have beneficial impact on women's health (61).

A comprehensive meta-analysis of cardiovascular risk markers in women with PCOS that included 130 data

sets in 11 different outcomes, has shown that women with PCOS demonstrated significantly elevated CRP, homocysteine, plasminogen activator inhibitor-I (PAI-I), PAI-I activity, vascular endothelial growth factor, asymmetric dimethylarginine, AGEs and lipoprotein(a) in comparison to controls, although with significant between-study heterogeneity (62). Borderline significance was detected for TNF alpha, endothelin-I and fibrinogen, whereas no significance was detected for interleukin-6. According to results of this meta-analysis, in light of the atherosclerotic process, PCOS is related not only to low-grade chronic overall and endothelial inflammation but also to coagulation abnormalities. Moreover, in this paper, a clinical interpretation of the results was attempted based on selected published evidence which elucidated that serum concentrations of cardiovascular risk markers are not negligible, being of similar order of magnitude to those in patients with established cardiovascular disease.

### Hyperandrogenism and cardiovascular risk in PCOS

Hyperandrogenism is associated with an adverse metabolic phenotype and an increased cardiovascular risk through complex and multidirectional pathways (63, 64). Exposure to hyperandrogenemia (either prenatally or as an adult) may influence body fat distribution, insulin resistance and other cardiometabolic risk features (65, 66). It was also shown that hyperandrogenemic women with PCOS have significantly higher liver fat content in comparison to normoandrogenemic PCOS and control women, which was independent of obesity and insulin resistance (67).

A study investigating different phenotypes of PCOS based on the Rotterdam criteria found that 'PO' phenotype did not differ significantly from control women in respect to insulin sensitivity, and these patients were significantly less insulin resistant than 'PHO' phenotype (68). It was also shown that obese normoandrogenemic women with PCOS had a relatively mild phenotype compared with obese hyperandrogenemic women with PCOS, based on 1990 NIH criteria (69).

As part of the Study of Women Across the Nation (SWAN), an analysis which included 3297 premenopausal and perimenopausal women of different ethnic groups (white, black, Hispanic, Chinese and Japanese) showed that low SHBG and high free androgen index are strongly and consistently related to increased cardiovascular disease risk factors (higher insulin, glucose, hemostatic and inflammatory markers and more adverse lipid

profile), even after controlling for body mass (39). The study concluded that androgens likely play a role in the cardiovascular risk profile of perimenopausal women.

Simultaneous measurement of serum testosterone and androstenedione represents a useful tool for predicting metabolic risk in PCOS women. A recent study has shown that serum androstenedione was a more sensitive indicator of PCOS-related androgen excess than serum total testosterone concentrations (70). Furthermore, this study demonstrated that PCOS patients with co-elevation of androstenedione and testosterone had impaired indices of insulin sensitivity compared with those with normal androgens or milder hyperandrogenemia. Moreover, multiple linear regression showed a strong negative association between serum androstenedione and insulin sensitivity. The incidence of dysglycemia according to an oral glucose tolerance test increased with the severity of androgen phenotype. Concurrent measurement of both androstenedione and testosterone discovers a PCOS cohort that appears to be at the highest metabolic risk.

However, a recent large prospective population-based cohort study in postmenopausal women from Rotterdam municipality, who had been free of cardiovascular disease at study entry, found no association between higher androgen levels in postmenopausal women and incident stroke, coronary heart disease or composite cardiovascular disease events, after adjustment for cardiovascular risk factors (71). Authors concluded that atherosclerosis burden among postmenopausal women might be caused largely by adverse cardiovascular risk factors, and hyperandrogenism *per se* might not be a risk factor for cardiovascular disease after menopause. The limitation of this study was rather small number of PCOS cases identified in the cohort of 2578 women (out of 272 with the history of irregular menses at 25 years of age only 106 also had testosterone or free androgen index levels in the highest quartile) and the possibility of selection bias as women with PCOS who had developed cardiovascular disease before the menopause or age 55 years were not eligible for the study.

### Genetic variants possibly affecting cardiovascular risk in PCOS

PCOS and its different phenotypes result from complex interactions between multiple genetic predisposing variants and environmental and lifestyle factors (2). Possible associations between several genetic polymorphisms in PCOS in relation to its metabolic

complications and possible cardiovascular risk have been investigated. In a study in North India, presence of metabolic syndrome or related metabolic derangements was found to be high in the family members of women with PCOS (72). In Spanish population, some of the calpain 10 (*CAPN10*) gene polymorphisms (this gene has been associated with the presence of metabolic syndrome in PCOS and type 2 diabetes) were found to be related to insulin resistance phenotypes (73). Also, a correlation between PAI-I promoter 4G/5G polymorphism and metabolic/proinflammatory factors in PCOS was reported (52).

In another report, the TAAAA repeat polymorphisms in the *SHBG* gene were studied. Although it was not shown to be a major determinant of the PCOS status, it influenced serum SHBG levels in PCOS patients. Moreover, a strong negative association was shown between serum SHBG and CRP, an established risk factor of cardiovascular disease and a marker of low-grade inflammation, typical of atherogenesis. This may be one of the pathways by which low SHBG levels affect cardiovascular risk (74).

In Chinese population, the platelet-activating factor acetylhydrolase (PAF-AH) gene polymorphisms in PCOS were analyzed. Increased plasma PAF-AH and apoB-PAF-AH activities in patients with H allele of R92H variant of the *PAF-AH* gene were reported to be associated with changes in plasma lipoprotein levels, insulin resistance, gaining weight and thus could be involved in the pathogenesis of PCOS and the increased risk of future cardiovascular disease (75).

Some studies did not confirm expected associations. In young Turkish patients, gene polymorphism of interleukin-6 (*IL6*) –174 G>C was found to be a risk factor for PCOS; however, no relationship was found between the cardiovascular risk factors and *IL6* –174 G>C gene and apolipoprotein E gene polymorphism in PCOS subjects (76, 77). In another study, an association between the *MTHFR* C677T gene polymorphism (which is a common genetic abnormality leading to hyperhomocysteinemia) and the development of metabolic syndrome in PCOS was not confirmed (78).

In research of cardiovascular disease, the candidate-wide association study showed that no loci were definitively identified with PCOS after strict correction for multiple testing, suggesting that cardiometabolic loci are not major risk factors underlying the susceptibility to PCOS (79). It is important to recognize that further research in this area is to be expected in the next years including larger sample sizes, which will help to further elucidate possible associations.

## Subclinical and clinical cardiovascular disease during the lifecourse of PCOS patients

### Early subclinical atherosclerotic disease in PCOS patients

Many studies have confirmed an association between PCOS and early, subclinical, reversible forms of vascular disease (80, 81, 82, 83, 84). It was shown that even young, normal-weight, non-dyslipidemic, non-hypertensive women with PCOS have an early impairment of endothelial structure and function (85); a finding that was later confirmed by meta-analysis of studies on endothelial dysfunction in PCOS as measured by flow-mediated dilation of the brachial artery (86). The meta-analysis on intima-media thickness of carotid arteries, another marker of subclinical atherosclerosis, has shown significantly increased values in women with PCOS compared with women without PCOS suggesting that women with PCOS are at a greater risk of premature atherosclerosis, which emphasizes the importance of screening and monitoring cardiovascular disease (CVD) risk factors in women with PCOS (87). Endothelial dysfunction in PCOS was found to be associated with higher levels of androgens and with insulin resistance (88, 89). This was observed even at very early ages, and with a trend of deterioration of endothelial function from lean to overweight and obese PCOS women, with excess visceral fat accumulation being a very important predictor of atherosclerosis in PCOS (32, 90, 91), although not all studies are consistent (92). In a similar study evaluating PCOS patients in different age groups (<20, 20–23.9, 24–28, >28 years), it was shown that with higher age insulin resistance increases in obese but not in lean and overweight women with PCOS (14). This study thus indicates that it is possible that women with PCOS that do not become obese may exhibit a better metabolic profile during their reproductive years.

Furthermore, besides endothelial dysfunction, PCOS women older than 30 years irrespective of BMI were found to have higher waist-to-hip ratio, systolic and diastolic blood pressure, total and LDL cholesterol, triglycerides and also ratios of total cholesterol/HDL cholesterol and triglycerides/HDL cholesterol, respectively (93).

### Clinical cardiovascular disease in PCOS patients

A very recent large national register-based study in Denmark that included 18,112 women with PCOS and 52,769 control women reported higher event rates

of cardiovascular disease including hypertension and dyslipidemia in relatively young PCOS patients compared to controls. The age at inclusion was median (quartiles) 29 (23–35) years, follow-up was 11.1 (6.9–16.0) years and the median age at diagnosis of cardiovascular disease was 35 (28–42) years in PCOS Denmark vs 36 (30–43) years in controls ( $P < 0.001$ ). Obesity, diabetes, infertility and previous use of oral contraceptives were associated with increased risk of development of cardiovascular disease in PCOS. Interestingly, no relation between total and free testosterone, and SHBG levels and cardiovascular disease was detected in the subgroup analysis of PCOS women in whom the biochemical data were available (94). In another study, middle-aged women with PCOS were found to be at increased risk of metabolic cardiovascular syndrome and had increased coronary artery and aortic calcification compared with controls, independently of obesity (84).

In 143 women aged 60 years or younger that underwent coronary angiography, those with more extensive coronary artery disease were more likely to have polycystic ovaries on ultrasonography than were those with less extensive disease (95). Increased coronary artery calcification in PCOS women in comparison to obese or non-obese women of similar age was also reported by another study (96).

The Nurses's Health Study included 82,439 female nurses who provided information in 1982 on prior menstrual regularity and were followed through 1996. It showed that women reporting irregular or very irregular cycles had an increased risk for nonfatal or fatal coronary heart disease with age-adjusted relative risks 1.25 and 1.67, respectively, which remained significant even after adjustment for BMI and several potential confounders. Increase in overall stroke risk and in ischemic stroke risk associated with very irregular cycles was insignificant (97).

A study of 786 women who received a diagnosis of PCOS in the United Kingdom before 1979 and were traced to investigate the long-term consequences of the syndrome 31 years later showed that in comparison to control group women with a history of PCOS had higher levels of several cardiovascular risk factors including diabetes, hypertension, raised plasma cholesterol and BMI  $> 30$ . Mortality and morbidity from coronary heart disease did not differ significantly between the women with PCOS and comparison groups (98).

A large cohort of 15,005 pregnant women recruited from the Kaiser Foundation Health Plan in California between 1959 and 1966 were matched to California Vital Status files annually until 2007 to identify deaths due to

overall cardiovascular disease and subsets of coronary heart disease. Compared with women with regular cycles, women with irregular cycles had an increased risk for coronary heart disease mortality; however, the association was not statistically significant after adjustment for BMI. There was a nonsignificant increase in cardiovascular disease mortality (99).

Another study that used data from claims of the Taiwan National Health Insurance, identified 8048 women aged 15–49 years diagnosed with PCOS and 32,192 women without the syndrome as controls. After a mean follow-up period of 5.9 years, the overall incidence of coronary artery disease was found to be 63% higher in women with PCOS. The incidence of coronary artery disease increased further in those with cardiometabolic comorbidities (100).

In a small, longitudinal study of PCOS ( $N = 25$ ) that followed women 21 years after the diagnosis (aged 61–79 at the time of analysis), it was shown that in comparison to the control group, PCOS women had a higher prevalence of hypertension and higher triglycerides (101). Myocardial infarction, stroke, diabetes, cancer and mortality prevalence were similar to age-matched controls. The previously mentioned large prospective population-based cohort study in postmenopausal women from Rotterdam could also not show increased morbidity and mortality from cardiovascular disease in the subcohort of women with PCOS, after adjusting for cardiovascular risk (71).

Another meta-analysis of five controlled observational studies published between 2000 and 2008 showed a relative risk for (non-)fatal coronary heart disease or stroke was 2.02 when comparing women with PCOS to women without PCOS; BMI adjustment did not affect this finding (102).

In summary, data from prospective end point trials about cardiovascular morbidity and mortality and from meta-analyses are scarce and controversial. Nevertheless, since the early phases of the atherosclerotic process have been well documented in PCOS women and are reversible before progressing to clinically important disease, it is reasonable to implement present knowledge of cardiovascular risk into clinical management of PCOS, especially regarding non-pharmacologic measures such as exercise and healthy lifestyle (103). At present, longitudinal screening for cardiometabolic risk factors in PCOS is recommended by guidelines of several international societies, including BMI, waist circumference, blood pressure, fasting lipid levels measurement and screening for impaired glucose tolerance and type 2 diabetes mellitus (103, 104, 105, 106). Assessment for cigarette smoking,

OSA, depression and anxiety is also advised, with further management of those if needed.

### Possible therapeutic interventions in PCOS with beneficial effects on cardiovascular and metabolic risk factors

Since PCOS is a complex polygenic disorder with important environmental influences, especially those that contribute to obesity (2), it should be stressed that there is a relative lack of systematic prospective studies investigating long-term effects of different lifestyle interventions in comparison to studies investigating pharmacological interventions.

Moreover, given the high prevalence of the syndrome, public media coverage, which was very efficient in educating the public about other diseases and health issues, such as diabetes, aids, smoking etc., is still insufficient in the case of PCOS. Several studies were published exploring the influence of public media coverage of other health issues (107, 108, 109). However, the only study exploring how digital (online) teen and women's magazines portray women with PCOS found that articles depicted PCOS symptoms only as a hindrance to women's social roles as wives and mothers and largely placed personal responsibility on women to improve their health (110). Moreover, experiences of Latin and African American women and adolescents with PCOS were absent from these articles. A systematic approach coordinated by international endocrine organizations would be prudent for adequate management of this large group of patients.

#### Diet

Positive effects of even 5–10% weight loss on reducing risk factors for cardiovascular disease, type 2 diabetes, endocrine and reproductive parameters in PCOS have been reported (111). A study investigating the effects of a high-protein, low-glycemic-load diet compared with a conventional hypocaloric diet on reproductive hormones, inflammatory markers, lipids, glucose and insulin levels in obese women with PCOS showed that both hypocaloric diets significantly reduced body weight and androgens. However, the combination of high-protein and low-glycemic-load foods in a modified diet caused a significant increase in insulin sensitivity and a decrease in high-sensitivity CRP (hsCRP) level when compared with a conventional diet (112). Another study in overweight and obese PCOS subjects investigated a Mediterranean-inspired

low-glycemic-load anti-inflammatory diet (based on combinations of nutrients; encouraging the consumption of legumes, fish and low-fat dairy products) and regular exercise (all participants were instructed to use the stairs to the upper floor up and down for 30 min/day, and three times 10 min/day of sit-ups or abdominal crunches) + five cups of green tea intake daily. After 12 weeks, they found moderate weight loss (6.3 kg or 7.2%) and significant improvements in body composition, hormones and menstrual cyclicity, blood pressure, glucose homeostasis, dyslipidemia, CRP and serum amyloid A (surrogate measures of cardiovascular risk) (113).

Vitamin D deficiency is reported to be common in PCOS (114). It may exacerbate symptoms of PCOS, with observational studies showing lower 25-OH-vitamin D levels to be associated with insulin resistance, ovulatory and menstrual irregularities, lower pregnancy success, hirsutism, hyperandrogenism, obesity and elevated cardiovascular disease risk factors. In a small interventional study, vitamin D therapy in PCOS patients was shown to have beneficial effect on some cardiovascular risk factors (decreased serum total cholesterol, triglycerides and very low-density lipoprotein (VLDL) but it did not affect serum HDL cholesterol, LDL cholesterol, apolipoprotein A1 and hsCRP concentrations (115). A recent meta-analysis found that lower serum vitamin D levels were related to metabolic and hormonal disorders in women with PCOS such as increased levels of fasting glucose and HOMA-IR compared to those without vitamin D deficiency (116). This meta-analysis found no evidence that vitamin D supplementation reduced metabolic and hormonal dysregulations in PCOS. Another systematic review also reported possible inverse association between vitamin D status and metabolic disturbances in PCOS but due to the heterogeneity of the studies omitted from drawing definite conclusions (117). Regarding possible beneficial effects of vitamin D supplementation on cardiovascular risk factors, we should acknowledge that current evidence is limited and further prospective randomized clinical trials are required.

#### Exercise/lifestyle modification

Supervised exercise (16 weeks) in women with PCOS improves endothelial function, an adaptation associated with reduced cardiovascular risk. This change occurs independently of changes in body weight or composition, which further stresses the fact that success of public health interventions in PCOS should not be solely judged by weight loss (118). A systematic review of the impact of

lifestyle modification interventions on outcomes of women with PCOS suggests that lifestyle modification reduces fasting blood glucose and insulin levels in women with PCOS with metformin having similar effects. Translation of these short-term effects to patient-important outcomes, beyond diabetes prevention, remains uncertain (119).

On the other hand, it was shown that exercise training (20 weeks) provided no additional benefit to following a high-protein, hypocaloric diet on markers of endothelial function in overweight/obese women with PCOS (120). In a small study, 40-min bout of aerobic exercise was reported to induce differential expression of insulin resistance-related genes in skeletal muscles of PCOS patients (121). It should be emphasized that all interventions in above studies were of relatively short duration. Further research should elucidate long-term effects of such interventions.

### Medical treatment

Metformin has been used as a treatment option for PCOS for two decades (122). Metformin increases insulin sensitivity by decreasing gluconeogenesis, lipogenesis and enhancing glucose uptake in the liver, skeletal muscle, adipose tissue and ovaries (123). It was shown to have beneficial effects on cardiovascular risk factors in PCOS (124, 125). In PCOS, it can be used as a single treatment or as part of a combination treatment. It was shown that variations in treatment response to metformin relate to differences in baseline BMI and testosterone levels in different PCOS patients (126). A recent meta-analysis investigating effects of metformin in PCOS that included 14 randomized clinical trials reported that treatment with metformin reduced BMI, waist-to-hip ratio, had a significant beneficial effect on systolic and diastolic blood pressure and triglyceride levels (but not on total, LDL and HDL cholesterol). In comparison to placebo, it did not significantly affect fasting blood glucose levels, HOMA-IR or fasting insulin. However, it significantly affected glucose insulin ratio (127).

Another meta-analysis showed that combination of lifestyle intervention (defined as any duration of diet, behavioral change, exercise) plus metformin for 6 months is associated with lower BMI and subcutaneous adipose tissue as compared to lifestyle plus placebo (128).

A study investigating oral contraception (ethinyl estradiol plus cyproterone acetate) effects vs combination of low-dose pioglitazone plus flutamide plus metformin for 18 months in non-obese adolescent girls with androgen excess found that both regimes attenuated androgen excess. However, during and 6 months after treatment,

the group treated with pioglitazone/flutamide/metformin had a lower glucose-induced insulinemia, lower CRP levels and thinner carotid intima-media thickness. Moreover, they had less visceral adipose tissue, had a higher lean mass. Six months after the treatment, they were more likely to have regular cycles in comparison to the group treated with oral contraception (129). Authors of the study emphasized that reducing androgen excess in adolescence influences the posttreatment phenotype – so the type of intervention chosen in adolescence holds the potential to prevent part of the androgen excess phenotype in adulthood including adiposity, subfertility and cardiovascular risk.

Glucagon-like peptide-1 receptor agonists that are used to treat type 2 diabetes and obesity have been explored in PCOS and have shown a beneficial effect on weight loss (130). However, they also have beneficial effects on cardiovascular system (131, 132). The possible beneficial effects of liraglutide treatment in PCOS on cardiovascular system have been explored in a rat model of PCOS treated for 4 weeks and showed improved glucose excursion during oral glucose tolerance test and lower blood pressure (rats were hypertensive before treatment) (133).

Another study showed that both metformin and exenatide treatments for 24 weeks were associated with weight loss; however, combination treatment had an additive effect (134). In this study, all subjects were insulin resistant at baseline – a greater improvement of HOMA-IR with combination therapy was found. However, there was a lack of statistically significant differences between two mono-treatment modalities.

A study investigating metformin-treated women with PCOS with persistent insulin resistance showed that add-on dipeptidyl dipeptidase-4 inhibitor alogliptin alone or in combination with pioglitazone improved beta cell function and insulin sensitivity (135).

Also oral spironolactone, an androgen receptor and mineralocorticoid receptor antagonist, is used in PCOS to reduce the growth of terminal hair (2). Our group was the first to report that spironolactone treatment improved endothelial dysfunction in non-obese, non-insulin-resistant PCOS patients (136).

Combined oral contraceptives are frequently used in PCOS due to their effectiveness in regulating menses (also reducing risk of endometrial hyperplasia) and reducing hirsutism (2). Concern has been raised that they could contribute to increased cardiovascular risk in PCOS by increasing blood pressure and triglyceride levels (106).

Furthermore, in PCOS, bariatric surgery can be effective in achieving significant weight loss, restoration



of the hypothalamic–pituitary–ovarian axis, reduction of cardiovascular risk and even in improving pregnancy outcomes (137). A recent meta-analysis indicated that surgically induced weight loss in women with severe obesity and PCOS resulted in marked decreases in serum levels of total and free testosterone and the resolution of hirsutism and menstrual dysfunction in as many as 53% and 96% of the patients, respectively, leading to a striking PCOS resolution rate of 96% (95% CI, 88–100%); however, whether PCOS might reappear in the patients who regain weight is currently unknown (138). Therefore, bariatric surgery should be considered as part of the treatment in obese PCOS women, especially in those with metabolic syndrome.

## Conclusion

The data are firm that women with PCOS represent a population with a high prevalence of metabolic disturbance and cardiovascular risk factors, with different PCOS phenotypes differing significantly in their risk that aggravates with severity of androgen excess. Therefore, besides treating the classical signs and symptoms of PCOS, management of these patients should also aim to improve metabolic and cardiovascular risk with lifestyle changes considered as a crucial part of treatment.

As data on cardiovascular morbidity and mortality in PCOS population of women are discordant, prospective long-term multicentric epidemiological studies, including women in early reproductive age and following them into late menopause when most cardiovascular events happen, are needed to clarify the controversial issues on morbidity and define the impact of hyperandrogenemia on cardiometabolic risk at different stages in life of PCOS women.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

### Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received in final form 14 May 2018

Accepted 29 May 2018

Accepted Preprint published online 29 May 2018