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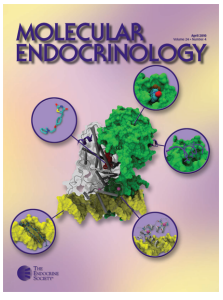

Assessment of Cardiovascular Risk and Prevention of Cardiovascular Disease in Women with the Polycystic Ovary Syndrome: A Consensus Statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society

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Objective: Women with polycystic ovary syndrome (PCOS) often have cardiovascular disease (CVD) risk factors. The Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society created a panel to provide evidence-based reviews of studies assessing PCOS-CVD risk relationships and to develop guidelines for preventing CVD.

Participants: An expert panel in PCOS and CVD reviewed literature and presented recommendations.

Evidence: Only studies comparing PCOS with control patients were included. All electronic databases were searched; reviews included individual studies/databases, systematic reviews, abstracts, and expert data. Articles were excluded if other hyperandrogenic disorders were not excluded, PCOS diagnosis was unclear, controls were not described, or methodology precluded evaluation. Inclusion/exclusion criteria were confirmed by at least two reviewers and arbitrated by a third.

Consensus Process: Systematic reviews of CVD risk factors were compiled and submitted for approval to the AE-PCOS Society Board.

Conclusions: Women with PCOS with obesity, cigarette smoking, dyslipidemia, hypertension, impaired glucose tolerance, and subclinical vascular disease are at risk, whereas those with metabolic syndrome and/or type 2 diabetes mellitus are at high risk for CVD. Body mass index, waist circumference, serum lipid/glucose, and blood pressure determinations are recommended for all women with PCOS, as is oral glucose tolerance testing in those with obesity, advanced age, personal history of gestational diabetes, or family history of type 2 diabetes mellitus. Mood disorder assessment is suggested in all PCOS patients. Lifestyle management is recommended for primary CVD prevention, targeting low-density and non-high-density lipoprotein cholesterol and adding insulin-sensitizing and other drugs if dyslipidemia or other risk factors persist. **(*J Clin Endocrinol Metab* 95: 2038–2049, 2010)**

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Abbreviations: BMI, Body mass index; BP, blood pressure; CAC, coronary artery calcification; CVD, cardiovascular disease; HDL, high-density lipoprotein; HDL-C, HDL-cholesterol; IGT, impaired glucose tolerance; IMT, intima-media thickness; IR, insulin resistance; LDL, low-density lipoprotein; LDL-C, LDL-cholesterol; MBS, metabolic syndrome; PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus.

Polycystic ovary syndrome (PCOS) is a common endocrinopathy affecting 6–10% of reproductive-aged women (1–3) and manifested by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries in its complete phenotype (4). Although evidence for cardiovascular events in women who were affected by PCOS during fertile age is limited (5), available data suggest more frequent cardiovascular disease (CVD) in classic PCOS (5). In young women with PCOS, multiple risk factors for CVD, including metabolic syndrome (MBS), type 2 diabetes mellitus (T2DM), dyslipidemia, abdominal obesity, and hypertension (5–7) may be found, and prevention of future cardiovascular adverse effects is needed. With increased adiposity in two thirds of American PCOS women (8), the degree to which obesity and PCOS interact to promote premature atherosclerosis and increase cardiovascular mortality is a worldwide concern (9–14).

Therefore, the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society appointed a panel to review all published evidence assessing CVD risk in PCOS *vs.* non-PCOS women and to recommend PCOS-related guidelines for CVD prevention. An important consideration was the broader definition of PCOS [*i.e.* Rotterdam 2003 (15) or AE-PCOS 2006 (4] *vs.* the more restrictive NIH 1990 criteria (16). The former non-NIH criteria include more women (17) and increase heterogeneity of PCOS phenotypic expression. The following statement provides consensus recommendations based on systematic reviews for screening and preventing CVD risk factors in PCOS.

Materials and Methods

Panel

The AE-PCOS Board appointed a panel of experts in PCOS and CVD. Panel members and Board Directors constituted the Writing Committee. No external funds were used.

Data

Systematic reviews of published peer-reviewed medical literature identified studies evaluating CVD risk factors for women (18) with and without PCOS. Multiple databases were queried, including MEDLINE, EMBASE, Cochrane, ERIC, EBSCO, dissertation abstracts, and current contents. Reviews evaluated prevalence of obesity, metabolic dysfunction, MBS, depression, inflammation, dyslipidemia, hypertension, physical inactivity, and interventions comparing PCOS *vs.* control women with and without weight matching. Articles were excluded by consensus if other hyperandrogenic disorders were not excluded, PCOS diagnosis was uncertain, controls were not described, or methodology precluded risk factor assessment. More than 1000 articles were initially available for review, with some studies eliminated because data were insufficient for epidemiological analysis or were reported in previous publications. All data sources were analyzed recognizing positive publication bias.

Process

The committee critiqued each review, considering Endocrine Society guidelines for primary CVD prevention in patients at metabolic risk, before submitting the manuscript to the AE-PCOS Society Board for approval (19). Reviews included individual studies, systematic reviews, hand searches, abstracts, and individual databases and expert data. Each systematic review was conducted by at least three investigators, and criteria for inclusion/exclusion were agreed upon by at least two reviewers in each area and arbitrated by a third when necessary. The position statement applied part of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group criteria (20, 21), in which strength of a recommendation was indicated "recommend" or a weaker recommendation was indicated "suggest." Recommendations were accompanied by evidence that was considered in making the recommendation. Institutional Review Board approval was not obtained because the study reviewed publicly available literature.

PCOS Phenotype

A crucial factor in assessing CVD risk for a woman with PCOS is the definition of PCOS itself (Table 1). When Rotterdam or AE-PCOS *vs.* "classic" NIH criteria are applied, the prevalence of PCOS in the population increases to over 20% (22), with approximately 75% of referred PCOS patients having classic PCOS and the remaining 25% evenly divided between ovulatory and nonhyperandrogenic PCOS phenotypes (23). Women with classic PCOS have greater menstrual irregularity, hyperandrogenism, total and abdominal obesity, and insulin resistance (IR) and have more severe risk factors for T2DM and CVD than PCOS patients diagnosed using non-NIH criteria (24–29). Ovulatory PCOS patients have lower body mass index (BMI) and abdominal obesity, lesser degrees of hyperandrogenism and hyperinsulinemia, reduced MBS

TABLE 1. Diagnostic criteria for PCOS

Criteria	NIH 1990 "classic"	Rotterdam 2003	AE-PCOS
Oligomenorrhea[a]	+	+/−	+/−
Clinical or biochemical hyperandrogenism[b]	+	+/−	+
Polycystic ovaries on ultrasound[c]	+/−	+/−	+/−

NIH, Presence of both oligomenorrhea and clinical/biochemical hyperandrogenism; Rotterdam, any two of the above criteria; AE-PCOS, presence of clinical/biochemical hyperandrogenism and one other criterion.

[a] Eight or less menses per year.

[b] Acne or hirsutism or androgenic alopecia.

[c] Ovarian volume >10 ml and/or >12 follicles less than 9 mm in size in at least one ovary.

prevalence, and milder forms of dyslipidemia (24–27, 29), whereas nonhyperandrogenic PCOS patients have the most metabolically favorable profile, often indistinguishable from normal women (25, 28, 30, 31).

CVD Risk Factors

Most CVD risk factor studies have been conducted in women with classic PCOS (NIH criteria), often before new criteria were developed, with several studies comparing PCOS and control women using BMI matching (14, 32–35). Differences between PCOS and control women exist in several CVD risk factors, which often are more profound in obese PCOS women (33, 35).

Impaired glucose tolerance (IGT)

IR occurs in approximately 60–80% of women with PCOS and in 95% of obese women with PCOS (36, 37). In most classic cases of PCOS, insulin-mediated glucose uptake is impaired, but the precise mechanism remains elusive (38, 39). These women with PCOS have IR independent and additive with that of obesity, with PCOS and obesity acting synergistically to impair insulin sensitivity (38).

Consequently, IGT and MBS, as predictors of T2DM and premature CVD mortality (40–42), are prevalent in women with PCOS (odds ratio, approximately 4:1) (43, 44). Alarmingly, IGT and T2DM are highly prevalent among PCOS adolescents (45), and, although incident data are not rigorous, up to 40% of women with classic PCOS develop IGT or T2DM by the fourth decade of life (46, 47), with age and weight gain worsening glycemic control (46–48). In one study, classic PCOS patients had a 5-fold risk of developing T2DM over 8 yr *vs.* age- and weight-matched controls (48), although only 12% of PCOS patients without obesity developed glucose abnormalities (47).

Dyslipidemia

Dyslipidemia is very common in PCOS patients (up to 70% in the United States) (33, 49) and may present with different patterns, including low levels of high-density lipoprotein (HDL)-cholesterol (HDL-C), increased values of triglycerides and total and low-density lipoprotein (LDL)-cholesterol (LDL-C), as well as altered LDL quality (7, 33, 49–52). These different patterns may be related to the associated effects of IR and hyperandrogenism that combine with environmental (diet, physical exercise) and genetic factors (51, 52).

The most common pattern is probably the so-called atherogenic lipoprotein phenotype that is characterized by hypertriglyceridemia, increased small dense LDL-C levels, and decreased HDL-C levels (53, 54). This lipid pattern is similar to that found in T2DM (55), and it is mainly the consequence of IR that impairs the ability of insulin to suppress lipolysis, thereby increasing mobilization of free fatty acids from adipose stores. Consequently, increased hepatic delivery of free fatty acids impairs insulin inhibition of hepatic very low-density lipoprotein 1 synthesis, causing altered catabolism of very low-density lipoprotein (55). Because excessive adipose tissue increases IR (56), this pattern is more common in obese patients with PCOS. It occurs in the United States in about 70% of women with classic PCOS (51, 57) but is less common in other countries where mean body weight is lower (51). However, also in Mediterranean countries, about one half of women with PCOS have low HDL-C and a small dense LDL phenotype (50, 51, 58). Therefore, it is not surprising that current diagnostic guidelines recommend measuring serum triglycerides and HDL-C, although only in obese PCOS women (15).

Many studies have shown that LDL-C also is increased in women with PCOS (6, 33, 51, 52). The prevalence of increased LDL-C in PCOS is generally lower than that found for the atherogenic dyslipidemia and ranges from 24 to 40% (51, 52), but it is less dependent on body weight and may be partially related to the hyperandrogenism (52, 59).

The available evidence shows that different lipid patterns may be present in women with PCOS. In addition, differences between diverse ethnic and geographical backgrounds cannot be fully explained by variations in body weight alone (51, 52) but are likely to depend on the combination of genetic, environmental, and hormonal factors. In support of this, nonobese women with PCOS also can have elevated levels of lipoprotein (a) (29), a stable, genetically and racially determined, lipid-rich, LDL-like lipoprotein that is metabolically distinct from LDL-C (60).

MBS

Linked with IR is MBS, defined as elevated blood pressure (BP) (≥130/85 mm Hg), increased waist circumference (≥88 cm, non-Asian; ≥80 cm, East/South Asian women), elevated fasting glucose (≥100 mg/dl), reduced HDL-C (≤50 mg/dl in women), and elevated triglyceride (≥150 mg/dl) levels (19). Central to MBS is abdominal adiposity, which in PCOS is increased *vs.* controls, even in some (27, 61, 62) but not all (63, 64) nonobese individuals. Abdominal adiposity in PCOS worsens with weight gain to increase the risk of cardiovascular death, after adjusting for BMI (64, 65). The estimated prevalence of MBS in classic PCOS in the United States is 33–47% (12, 33, 43, 66, 67), about two to three times higher than that of age-matched controls (34, 66–68) and 13.7 times more likely in women with PCOS in the highest *vs.* the lowest BMI

quartile (66). In other countries, the prevalence of MBS is lower, ranging between 8 and 25% in women with classic PCOS (69, 70). Although the prevalence of MBS is high in PCOS, adjusting for BMI, it is lower if there is not excessive abdominal adiposity (66, 71).

Accompanying MBS in PCOS is an inflammatory atherothrombotic IR that elevates several proinflammatory substances (C-reactive protein, fibrinogen, white blood cells, plasminogen activator inhibitor-1, and endothelin-1), which impair endothelial function, reduce vasoreactivity, and promote subclinical atherosclerosis (72, 73).

Depression, anxiety, and reduced quality of life

There is growing evidence that mood disturbances, mostly severe depression, are independent CVD risk factors (18) and prevalent in women with PCOS (74, 75). Several studies show increased depression and anxiety in PCOS patients (74–77), in whom impaired quality of life from body image concerns cause fatigue, sleep disturbances, phobia, appetite changes, and binge eating (75–77). As a result, depressed women with PCOS have higher BMI and greater IR as CVD risk factors than nondepressed women with PCOS without differences in androgen excess (76), whereas weight loss through an energy-restricted diet improves their depression and quality of life (78). It remains to be determined how mood disturbances as CVD risk factors are linked with altered stress reactivity in women with PCOS, as evidenced by exaggerated ACTH and cortisol stress responses (79), impaired IL-6 up-regulation after stress (79), and heightened sympathetic nerve activity (80).

CVD Outcomes

Markers of atherosclerosis

Women with PCOS have more subclinical vascular disease *vs.* controls, adjusting for age and BMI. Wild *et al.* (81) found that increased waist/hip ratio and hirsutism were associated with confirmed coronary artery disease in women age 60 yr or older undergoing coronary angiography. Birdsall *et al.* (9) evaluated 143 women younger than 60 yr undergoing coronary angiography for chest pain or valvular disease and detected polycystic ovaries in 42% of these women, although NIH or Rotterdam criteria were not applied. Women with PCOS had more advanced coronary artery disease than women with normal ovaries.

Guzick *et al.* (10) evaluated 16 hyperandrogenic premenopausal women at least 40 yr of age, diagnosed previously with PCOS, compared with 16 age-matched regularly cycling controls undergoing carotid artery scanning and found mean carotid intima-media thickness (IMT) significantly greater in PCOS patients (0.68 mm) than controls (0.63 mm). Talbott *et al.* (82) evaluated 125 Caucasian women with PCOS and 142 age-matched controls and confirmed greater carotid-IMT in PCOS patients (0.78 mm) than controls 45 yr of age and older (0.70 mm), which remained significant after adjusting for BMI. Other studies have shown increased carotid-IMT in overweight and normal-weight women with PCOS (83, 84).

Two studies have measured coronary artery calcification (CAC), a marker of subclinical coronary atherosclerosis (13, 34). Using NIH criteria and adjusting for age and BMI, both studies suggest that women with PCOS have a greater CAC prevalence than controls, independent of age and BMI, although small sample sizes and the young age of the population precluded analysis of a range of CAC levels.

Cardiovascular events

Evidence for increased CVD morbidity and mortality is inconclusive, yet suggestive, given challenges with the current epidemiological studies. Of eight studies (11, 12, 14, 32, 85–88), four used Rotterdam and/or NIH criteria for PCOS and followed PCOS cases for CVD endpoints; designs are cross-sectional with small numbers (32, 85) or prospective with larger numbers (11, 12).

Initial studies did not find an increased prevalence of nonfatal/fatal CVD in women with PCOS (11, 12), although risk for nonfatal cerebrovascular disease appeared to be higher (12). However, a recent substudy of the Women's Ischemia Evaluation Study (WISE) (14) confirmed that women with PCOS have a larger number of cardiovascular events. In this study, multivessel CVD was observed in 32% of PCOS women compared with 25% of non-PCOS women (odds ratio, 1.7) and correlated with several factors, including increased free testosterone. In addition, the event free survival (including fatal and nonfatal events) was significantly lower in PCOS compared with non-PCOS women. The difference between the two groups was higher when cerebrovascular accidents were considered too, confirming the association of PCOS with stroke.

Two additional studies give further support to the association between PCOS and CVD. Krentz *et al.* (87) conducted a cross-sectional study of 713 postmenopausal women (mean age, 73.8 yr) and found in nondiabetic women with intact ovaries a stepwise graded association between CVD and numbers of features of putative PCOS, as defined by premenopausal menstrual irregularity, hirsutism, or current biochemical hyperandrogenism. Azevedo *et al.* (88) performed a case-control study of 414 postmenopausal women (mean age, 60.4 yr) and also noted in women with premenopausal menstrual irregularity (as a putative sign of PCOS) an increased odds ratio for coronary vascular disease.

In toto, the present epidemiological data suggest more frequent CVD in classic PCOS, mostly mediated through increased total and abdominal adiposity, and perhaps interacting with PCOS-related hyperandrogenism.

Assessing CVD Risk Factors in PCOS

Because lifetime risk for CVD in all women is high and mostly preventable, all women should be screened for CVD risk factors (89). Evidence-based guidelines for women provided by the American Heart Association (AHA) (89) classify women for CVD risk as: 1) optimal risk; 2) at risk; or 3) at high risk.

Recognizing that PCOS women with increased adiposity are at greater risk for T2DM, stroke, and CVD, the committee *recommends* that PCOS-related CVD risk be categorized as:

1. At risk—PCOS women with any following risk factors:
   - Obesity (especially increased abdominal adiposity)
   - Cigarette smoking
   - Hypertension
   - Dyslipidemia (increased LDL-C and/or non-HDL-C)
   - Subclinical vascular disease
   - IGT
   - Family history of premature CVD (<55 yr of age in male relative, <65 yr of age in female relative) (89), or
2. At high risk—PCOS women with:
   - MBS
   - T2DM
   - Overt vascular or renal disease

Because adolescent PCOS women acquire IR (90) as an antecedent to T2DM and CVD, lifetime CVD prevention strategies are of greater value for younger than older women (18). Therefore, all women with PCOS should be assessed for CVD risk. Accordingly, we *recommend* that:

1. Waist circumference and BMI be determined at every visit (19), using the National Health and Nutrition Examination Survey method, which is easy to perform, valid, and reproducible. Waist circumference is measured at the top of the iliac crest with the patient standing, using a nonfolded tape held parallel to the ground at the end of expiration. A waist circumference of at least 88 cm (35 inches) in Caucasian/African-American women or at least 80 cm (31.5 inches) in Hispanic, Native American, Asian (East and South), and European women is the easiest way to establish the presence of abdominal obesity (19).
2. A complete lipid profile (total cholesterol, LDL-C, non-HDL-C, HDL-C, and triglycerides) be determined. Based upon AHA guidelines (Table 2) (89), if the fasting serum lipid profile is normal, we suggest that it be reassessed every 2 yr or sooner if weight gain occurs. The primary target goal is LDL-C, with non-HDL-C estimating numbers of circulating small and large LDL particles as the secondary target for lifestyle and medical therapy (19, 89). We recommend that in women with PCOS without additional CVD risk factors, LDL-C levels should be less than 130 mg/dl (3.37 mmol/liter). Those with MBS or T2DM/overt vascular/renal disease should have serum LDL-C levels less than 70–100 mg/dl (1.81–2.59 mmol/liter) or 70 mg/dl (1.81 mmol/liter), respectively (89). Optimal (target) serum non-HDL-C levels should be 30 mg/dl (0.77 mmol/liter) higher than the designated LDL-C goal (Table 2); serum triglyceride levels, as an independent CVD risk factor in women, should be less than 150 mg/dl (89).
   Routine use of LDL subfractions appears premature (91) because it is unclear whether there is added benefit to traditional risk factor assessment. Routine apolipoprotein B testing is not recommended until it becomes universally standardized, although apolipoprotein B levels may be more accurate than non-HDL-C as a CVD risk predictor (92).
3. A 2-h post 75-g oral glucose challenge be performed in PCOS women with a BMI greater than 30 kg/m^2, or alternatively in lean PCOS women with advanced age (>40 yr), personal history of gestational diabetes, or family history of T2DM (44, 93). This outpatient test appears to be the best screening tool to detect IGT or T2DM in women with PCOS, who often have a normal fasting glucose (44). We *suggest* that patients with normal glucose tolerance be rescreened every 2 yr or sooner if additional risk factors are identified. Those with IGT should be screened annually for developing T2DM (93), acknowledging efficacy of treating IGT, but not necessarily impaired fasting glucose, to prevent T2DM (93).
   Hemoglobin A1c above 6.5% has been proposed as the defining criterion for diabetes (94). We endorse this criterion for risk assessment, but further studies will be needed to determine whether this criterion is useful in implementing lifestyle interventions and medical management for CVD prevention.
4. That BP be routinely checked at each visit. Ideal BP is 120 mm Hg systolic and 80 mm Hg diastolic or lower, and prehypertension should be detected and treated (95). BP control has the largest benefit for reducing CVD.

TABLE 2. PCOS risk categories and lipid target values[a]

	Risk	LDL target values, mg/dl (mmol/liter)[b]	Non-HDL target values, mg/dl (mmol/liter)[b]
PCOS	At optimal risk	≤130 (3.37)	≤160 (4.14)
PCOS with obesity, hypertension, dyslipidemia, cigarette smoking, IGT, subclinical vascular disease	At risk	≤130 (3.37)	≤160 (4.14)
PCOS with MBS	High risk	≤100 (2.59)	≤130 (3.37)
PCOS with MBS and other risk factors,[c] or with T2DM, or in presence of overt vascular and/or renal disease		≤70 (1.81)	≤100 (2.59)

[a] Values are based on at least 12-h fasting lipid determinations. Predictive utility for CVD events based on nonfasting lipoprotein lipid values has not yet been clearly validated.

[b] To convert mg/dl to mmol/liter, divide by 39.

[c] Odds of CVD increase with number of MBS components and with other risk factors, including smoking, poor diet, physical inactivity, obesity, family history of premature CVD (<55 yr of age in male relative, <65 yr of age in female relative) and subclinical vascular disease.

In addition, we *suggest* that women with PCOS be assessed for depression, anxiety, and quality of life.

Primary Prevention of CVD in PCOS

Lifestyle modification

The committee recommends lifestyle modification as first-line therapy for safety, public health benefit, and avoidance of risks and side effects of drug use. For overweight/obese women with PCOS, lifestyle modification, including diet, exercise, smoking cessation, and behavioral techniques (96), can be used to reduce CVD risk (97). It has been shown that short-term weight-loss intervention in PCOS women decreases abdominal fat (98, 99) and reduces androgenicity (98, 100) and IR (98, 99); it also improves dyslipidemia (99), depression, and quality of life (78), although long-term weight loss is unlikely (96). In two large intervention studies, almost 60% relative risk reduction in conversion to diabetes mellitus occurred in obese individuals (BMI, >30 kg/m^2) with IGT randomized to intensive lifestyle modification to reduce body weight by 5–7% (101, 102); less dramatic improvement occurred in less obese individuals (BMI, 25–30 kg/m^2) (93). Lifestyle modification is recommended as first-line therapy for all women with PCOS and is particularly important for those individuals with serum LDL-C levels greater than 160 mg/dl and/or non-HDL-C levels of at least 190 mg/dl (89).

A hypocaloric, low saturated fat, increased mono- and polyunsaturated fat diet (500–1000 kcal/d reduction; <30% calories from fat, <10% calories from saturated fat; increased consumption of fiber, whole-grain breads, cereals, fruits, and vegetables) is recommended, along with at least 30 min of moderate-intensity physical activity daily (93, 96, 101, 103) to maintain weight. Together, both reduce BMI and improve IR and cardiopulmonary function in overweight PCOS women (104) and provide greater reductions in fat mass in PCOS women (105). Modifying dietary macronutrient composition does not offer benefit for weight loss over conventional dietary approaches alone (103).

We suggest that overweight/obese PCOS women should initially attempt 5–10% weight loss to reduce obesity-related CVD risk factors, with long-term goals of achieving and maintaining reduced weight of 10 to 20% and a waist circumference of less than 88–80 cm, depending upon ethnicity (19) (Table 3).

TABLE 3. Lifestyle strategies and effectiveness for LDL reduction

Dietary factor	Dietary change	% estimated LDL reduction
Reduced saturated fat	Reduce saturated fat to 7% of total energy	8–10
Reduced trans fat	Reduce trans fat to 1% of total energy	2
Reduced dietary cholesterol	Reduce dietary cholesterol to <200 mg/d	3–5
Added plant stanols/sterols	Add plant stanols (2 g/d)	6–10
Added dietary fiber	Add viscous fiber (5–10 g/d)	3–5
Reduced weight	Reduce body weight by 7–10%	5–8
Total improvement		25–35

Modified from Ref. 19.

An individualized exercise program assures optimal compliance and includes group or home exercise and walking (10,000 steps = 30 min daily exercise; 15,000 steps are usually needed for weight loss). Even without weight loss, sedentary women with PCOS undergoing moderate-intensity exercise experience improved IR and dyslipidemia (106). Screening for premature CVD is important before initiating exercise. Cardiac stress testing should be performed if cardiac symptoms exist. Exercise should begin slowly to avoid physical stress (107).

Successful lifestyle management requires self-esteem and motivation (108, 109). Validated tools for screening, treating, and monitoring depression, abnormal eating patterns, and reduced life quality may be necessary for improving psychological symptoms and lifestyle management.

Medical therapy

Insulin sensitizers

Data regarding the effects of metformin on primary prevention of CVD are not consistent (110–118). Metformin has a small effect on body weight (less than 2–3% of BMI) (110, 112, 117) and may improve atherogenic dyslipidemia, increasing HDL-C and decreasing triglycerides (112, 114). However, in some studies, no changes in HDL-C or triglycerides were observed (115, 116). Metformin does not improve LDL-C or non-HDL-C (112, 114, 116) and should not be used when these lipid parameters are elevated. Metformin decreases circulating C-reactive protein (111) and may improve subclinical atherosclerosis, reducing carotid IMT and improving endothelial function (113, 118). The addition of metformin to lifestyle modification may be considered in those women who have MBS or subclinical atherosclerotic CVD, although more studies are needed to confirm this benefit. Medical treatment is not recommended for women with PCOS who have isolated hypertriglyceridemia and/or decreased HDL-C but do not have MBS or for those who are not considered to be at risk or at high risk.

The Committee suggests the use of metformin only in women with PCOS who are already undergoing lifestyle treatment and do not have improvement in IGT and in those women with IGT who are of normal weight, where weight loss in not appropriate. Although combined metformin/lifestyle modification to prevent T2DM in PCOS has not been established prospectively, small studies show that almost 30% of reproductive-aged women with PCOS have IGT, of whom one half revert to normal glucose tolerance with metformin (119–121). Improved glucose tolerance also has been shown in nonobese women with PCOS with IGT receiving thiazolidinediones (122), although increased bone fracture risk and exacerbation of preexisting congestive heart failure limit thiazolidinedione use for primary CVD prevention (19). Whether metformin should be used in PCOS to prevent conversion of normal glucose tolerance to IGT is debatable (46, 121).

Cholesterol-lowering drugs

Cholesterol-lowering drug therapy should be reserved for those patients with PCOS who have increased serum LDL-C and/or non-HDL-C levels. Intensity of cholesterol-lowering therapy should be adjusted to absolute lifetime risk of CVD (19, 123). Adult Treatment Panel III guidelines recommend reserving cholesterol-lowering drugs for women with serum LDL-C levels greater than 160 mg/dl and/or non-HDL-C levels of at least 190 mg/dl, regardless of age or ethnicity, although these drugs can be administered if LDL-C levels remain above 130 mg/dl (with at least two risk factors) despite 3 months of lifestyle modification (19). Lowering LDL-C levels to less than 70–100 mg/dl is appropriate for high-risk patients with MBS, T2DM, or overt vascular/renal disease (Table 2) (19, 89). Serum lipid levels can be repeated 6 wk after initiating therapy.

Although several lipid-lowering drugs exist and may be used (19, 124), only statins have been adequately studied in women with PCOS and have been shown to effectively lower LDL-C levels (116, 125). Several studies have shown that, in women with PCOS, statins diminish IR and inflammation, lower serum total and free testosterone levels, and improve endothelial dysfunction (116, 125–127). However, their use in pregnancy is contraindicated, and contraception is required.

In selected patients with severe dyslipidemia that is not adequately corrected by lifestyle modification and statins, dual pharmacotherapy may be required. It has been shown that the addition of metformin does not improve lipid levels further (116). Statins combined with a fibrate may be necessary when hypertriglyceridemia and low HDL levels coexist. Fenofibrate is preferred because of fewer drug interactions and the decreased risk of myopathy (19, 128). Nicotinic acid produces a favorable lipoprotein effect but requires careful monitoring for worsening glycemic control (19). Omega-3 fatty acids (4 g daily, pharmacy grade) are Food and Drug Administration (FDA) approved for serum triglyceride levels greater than 500 mg/dl (89).

Antihypertensives

Pharmacotherapy is indicated for BP of at least 140 mm Hg systolic or 90 mm Hg diastolic (19). Because milder forms of elevated BP (or prehypertension) increase CVD risk, reducing BP to 120/80 mm Hg is optimal for long-term CVD prevention (19). The committee recommends combining pharmacotherapy with lifestyle modification for persistent hypertension in PCOS women, recognizing that multiple drug therapy is often required. Although

some investigators favor angiotensin-converting enzyme inhibitors and angiotensin receptor blockers over diuretics and beta-blockers, use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, as with diuretics and beta-blockers, is contraindicated in pregnancy and requires contraception.

Antiobesity drugs

Phenteramine, sibutramine, and orlistat are FDA-approved weight loss medications. Some studies have shown that sibutramine combined with a hypocaloric diet improves weight loss, IR, and hypertriglyceridemia, as well as reducing serum free testosterone levels, more than hypocaloric diet alone (129, 130), but this drug may increase diastolic BP and heart rate (131) and is not approved during pregnancy. Orlistat induces a small weight reduction but without changing glucose-insulin homeostasis or lipid patterns (132). Because in PCOS the clinical experience with these agents is limited (103) and significant side effects may occur, the Committee does not recommend the use of weight loss medications in PCOS.

Bariatric surgery

Bariatric surgery may induce a significant weight loss (up to 60%) (133) and improve diabetes, hypertension, and dyslipidemia, reducing mortality from CVD and cancer when compared with lifestyle modification. Long-term weight loss has been shown to be a reduction of 14–25% (134, 135). In women with PCOS, bariatric surgery has been shown to be effective (136, 137). In 12 morbidly obese women with PCOS, an average weight loss of 41 kg in 1 yr postoperatively improved hyperandrogenism, IR, dyslipidemia, and hypertension and reversed the PCOS diagnosis (137).

Bariatric surgery may be an option for severely obese women with PCOS, in whom long-term diet-based strategies are seldom successful (103, 138, 139). Surgically induced weight loss, however, must be balanced against the risks of surgery, including a 0.1–1.1% mortality rate, bowel obstruction, infection, esophagitis, and nutritional abnormalities (133) and should be performed only after standard weight loss strategies have failed in PCOS women with a BMI greater than 40 kg/m^2 or greater than 35 kg/m^2 with a high-risk obesity-related condition (139).

Disclaimer

These Guidelines are not inclusive of all proper approaches or methods or exclusive of others and do not guarantee outcome or establish standards of care. They do not dictate treatment, which depends upon independent judgment for each patient. The AE-PCOS Society makes no warranty, expressed or implied, regarding the Guidelines and excludes any warranties of merchantability and fitness for particular use, and shall not be liable for damages from use of information contained herein.

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