Cardiometabolic Aspects of the Polycystic Ovary Syndrome

Harpal S. Randeva, Bee K. Tan, Martin O. Weickert, Konstantinos Lois, John E. Nestler, Naveed Sattar, and Hendrik Lehnert

Division of Metabolic and Vascular Health (H.S.R., B.K.T., M.O.W., K.L., H.L.), Warwick Medical School, University of Warwick, Coventry CV4 7AL, United Kingdom; Endocrine Unit (K.L.), Second Department of Obstetrics and Gynaecology, Aretceion University Hospital, Athens Medical School, 10676 Athens, Greece; Department of Internal Medicine (J.E.N.), Virginia Commonwealth University, Richmond, Virginia 23284; Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism (H.S.R., M.O.W.), University Hospitals Coventry and Warwickshire NHS Trust, Coventry CV2 2DX, United Kingdom; and Division of Cardiovascular and Medical Sciences (N.S.), University of Glasgow, Glasgow Royal Infirmary, Glasgow G31 2, Scotland, United Kingdom

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder amongst women of reproductive age and is associated with various metabolic perturbations, in addition to chronic anovulation and factors related to androgen excess. In general, women live longer than men and develop cardiovascular disease at an older age. However, women with PCOS, as compared with age- and body mass index-matched women without the syndrome, appear to have a higher risk of insulin resistance, hyperinsulinemia, glucose intolerance, dyslipidemia, and an increased prothrombotic state, possibly resulting in a higher rate of type 2 diabetes mellitus, fatty liver disease, subclinical atherosclerosis, vascular dysfunction, and finally cardiovascular disease and mortality. Further alterations in PCOS include an increased prevalence of sleep apnea, as well as various changes in the secretion and/or function of adipokines, adipose tissue-derived proinflammatory factors and gut hormones, all of them with direct or indirect influences on the complex signaling network that regulates metabolism, insulin sensitivity, and energy homeostasis. Reviews on the cardiometabolic aspects of PCOS are rare, and our knowledge from recent studies is expanding rapidly. Therefore, it is the aim of the present review to discuss and to summarize the current knowledge, focusing on the alterations of cardiometabolic factors in women with PCOS. Further insight into this network of factors may facilitate finding therapeutic targets that should ameliorate not only ovarian dysfunction but also the various cardiometabolic alterations related to the syndrome. **(*Endocrine Reviews* 33: 812–841, 2012)**

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Abbreviations: ADMA, Asymmetric dimethylarginine; ASAA, acute-phase serum amyloid; BMI, body mass index; CI, confidence interval; CPAP, continuous positive airway pressure; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density lipoprotein; HDL-C, HDL-cholesterol; IGT, impaired glucose tolerance; IMT, intima-media thickness; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatosis hepatitis; NP, natriuretic peptide; OC, oral contraceptive; OCP, OC pill; OSA, obstructive sleep apnea; PAI-1, plasma activator inhibitor-1; PCOS, polycystic ovary syndrome.

I. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, and it remains a diagnosis of exclusion. More recent studies have reported a prevalence of between 5 and 10% (1, 2). The prevalence and characteristics of women with PCOS among broader, ethnically diverse populations are less well understood.

In addition to chronic anovulation and androgen excess concerns, PCOS is also associated with a number of metabolic perturbations. These women have an increased risk of insulin resistance and hyperinsulinemia, an increased risk of glucose intolerance and type 2 diabetes mellitus (DM), dyslipidemia, subclinical atherosclerosis, and vascular dysfunction, independent of body mass index (BMI) (3) (Fig. 1). Furthermore, in overweight and obese PCOS women, these metabolic perturbations are accelerated, all of which may ultimately contribute to an excess risk for cardiovascular events.

Figure 1.

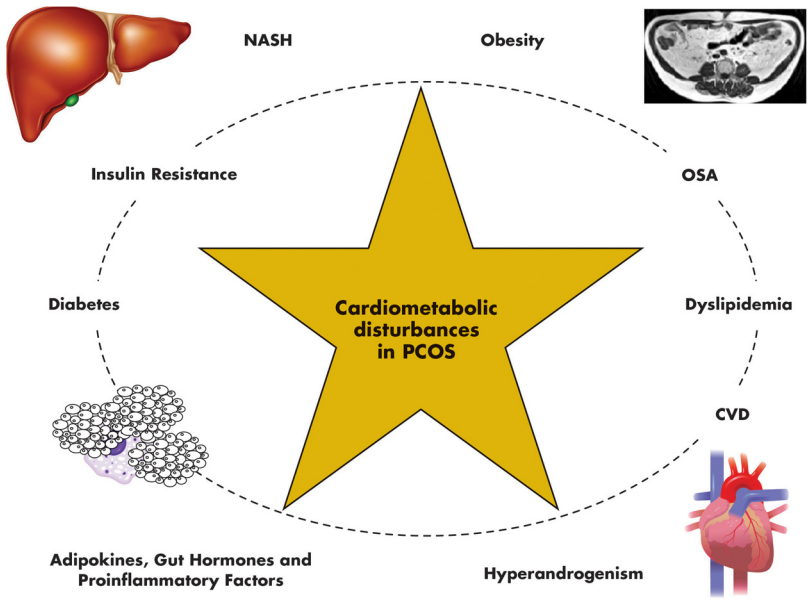

Figure 1. Cardiometabolic disturbances in PCOS. These include insulin resistance, hyperandrogenism, dyslipidemia, and alterations of the secretion and/or metabolic action of various adipokines, proinflammatory markers, and gut hormones, which may finally contribute to the observed increased prevalence of obesity, type 2 diabetes, NASH, OSA, and CVD in women with PCOS. However, for many of these factors, it remains to be determined whether they are causally involved in the pathogenesis of the syndrome or, alternatively, represent a consequence of changes in other factors.

Few previous reviews have focused on the cardiometabolic aspects in PCOS (4–7). Although there is a paucity of data in regard to cardiovascular event rates and mortality in PCOS, an increased prevalence of cardiovascular risk factors and changes in potential modulators of cardiovascular risk have been well documented. Here, we review novel aspects and mechanisms related to the spectrum of metabolic and cardiovascular risk modulators in PCOS.

II. Methods

We reviewed recent publications (up to April 2012) in the subjects of endocrinology, reproductive medicine and gynecology. EMBASE, ERIC, Cochrane, PubMed, and EBSCO were searched with a combination of query terms that included "PCOS," "cardiometabolic," "cardiovascular disease," "metabolic syndrome," "insulin resistance," "dyslipidemia," "adipokines," "gut hormones," "proinflammatory factors," "sleep apnoea," "NASH," "obesity," and many others that were assumed to be relevant. Relevant articles were also selected among references in published papers. Using these search criteria, more than 1500 relevant original papers and review articles were identified, with some overlap when using different search criteria. Due to constraints on the number of references, we then hand-selected studies and review articles covering the respective areas, excluding articles that provided similar information as compared with the selected ones and those where the diagnosis of PCOS was uncertain. When there were data available from larger or more robust trials, we also excluded studies that had small sample sizes, and therefore were likely underpowered to detect differences, and studies that showed high losses to follow-up and/or differential losses between the comparison groups.

III. Definition and Diagnostic Criteria of PCOS

Previously, the diagnosis of PCOS was based on National Institutes of Health (NIH) criteria including chronic anovulation and hyperandrogenism or on sonographic criteria (8). The more recent Rotterdam consensus meeting on

Figure 2.

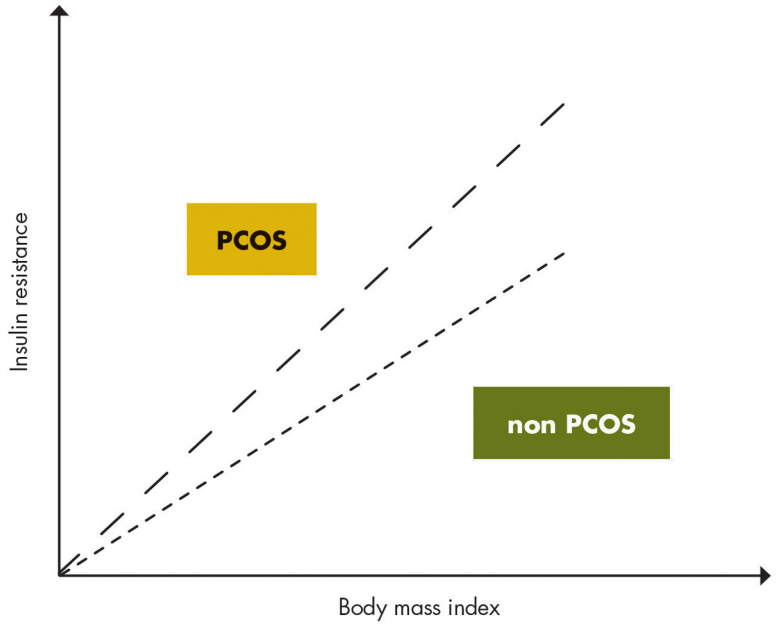

Figure 2. Relationship between BMI and insulin resistance in women with and without PCOS. Obesity and the PCOS status *per se* appear to be at least in part independent factors that contribute to the observed higher prevalence of insulin resistance and the metabolic syndrome in women with PCOS (33, 35); with increasing BMI, women with PCOS, compared with BMI-matched non-PCOS women, appear to accrue more metabolic abnormalities, likely contributing to the frequently observed higher insulin resistance in women with the syndrome. [Modified from N. Sattar: Polycystic ovary syndrome. *The metabolic syndrome*, 2nd ed. (edited by C. D. Byrne and S. H. Wild), Wiley-Blackwell, Oxford, UK, 2011 (171), with permission.]

PCOS between the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (9) revised the diagnostic criteria for PCOS as follows (two out of three): 1) oligo- or anovulation; 2) clinical and/or biochemical signs of hyperandrogenism (and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome); and 3) polycystic ovaries.

This revision represents an important progress due to higher flexibility, allowing a diagnosis of PCOS also, *e.g.*, in ovulatory hyperandrogenic or anovulatory normoandrogenic women with polycystic ovaries (8). This has led to a broader criterion for the diagnosis of PCOS that may impact on its perceived prevalence. However, the Rotterdam criteria have also been criticized for including more mild phenotypes, for example the combination of polycystic ovaries with oligomenorrhea, whereas women fulfilling the NIH criteria generally show a higher degree of metabolic derangements (10, 11). Further characterization of phenotypic differences in women with PCOS (12) with their respective therapeutic consequences is an important area for ongoing research.

IV. Hyperinsulinemia, Insulin Resistance, and Dysglycemia

There is a greater frequency and degree of both hyperinsulinemia and insulin resistance in PCOS (13). This insulin resistance appears to be at least in part independent of the effect of obesity, with both lean (30%) and obese women (70%) with PCOS showing decreased insulin sensitivity compared with age- and weight-matched normal women (Fig. 2). However, obesity exacerbates insulin resistance in PCOS (9, 13). In lean PCOS women, hyperinsulinemia is often evident postprandially (14) but not in the fasted state. Impaired glucose tolerance in the presence of normal fasting glucose is generally more frequently observed in females compared with males (15), with the relevant implication that impaired glucose metabolism in women, including women with PCOS, is often missed when using fasting glucose only as a diagnostic criterion, as opposed to using an oral glucose tolerance test (16). There is an increase in both impaired glucose tolerance and type 2 diabetes in PCOS: 31.1% of subjects had impaired glucose intolerance, and 7.5% had diabetes in a prospective study of 254 PCOS women; this is a 3- to 7-fold greater risk than the age-comparable population, and around a 2-fold higher risk compared with age- and BMI-comparable women with normal cycles (17). These findings have been corroborated elsewhere (18) and are further confirmed by a recent meta-analysis showing a higher than expected prevalence of impaired glucose metabolism and type 2 diabetes in women with PCOS, both in unmatched studies and when compared with age- and weight-matched women without PCOS (19). There also appears to be a risk of persistent impaired glucose metabolism after gestational diabetes in women with PCOS (20), as well as a high risk for glucose intolerance and diabetes in first-degree relatives of patients with PCOS (21).

Moreover, the vast majority of women with PCOS noted to have frank diabetes had a BMI greater than 30 kg/m^2. The strong link between insulin resistance and PCOS becomes also apparent from the trend of PCOS women to develop gestational diabetes (~10-fold) and other severe insulin resistance-related gestational compli-

cations such as spontaneous abortion (~3- to 5-fold increase). With regard to mortality rates, diabetes may be a more prominent contributing cause of death in women with PCOS compared with the general population (22), although morbidity and mortality from coronary heart disease among women with PCOS is not as high as previously predicted (22), probably reflecting the characteristic endocrine profile of women with PCOS that may protect against circulatory disease in this condition (23). Still, PCOS is considered an independent risk factor for type 2 diabetes in middle age (Clinical green top guidelines, RCOG, available at http://www.rcog.org.uk/womens-health).

The potential mechanisms leading to insulin resistance in PCOS need to be further defined, but it is suggested that postreceptor defects in the insulin receptor signal transduction are involved because no structural abnormality in the insulin receptor has been identified (25). Dunaif *et al.* (26) found that increasing the insulin receptor serine phosphorylation decreases its protein kinase activity, leading to insulin resistance in PCOS. Serine phosphorylation also appears to modulate the activity of the key regulatory enzyme of androgen biosynthesis, P450c17, present in both the adrenal and ovarian steroidogenic tissue, resulting in increased androgen synthesis (27). Thus, defective serine phosphorylation plausibly produces both the insulin resistance and the hyperandrogenism in a subgroup of PCOS women.

Chronic hyperinsulinemia may play further important roles in the modulation of cardiovascular risk. Natriuretic peptides (NP) are secreted from cardiomyocytes and directly influence blood pressure, body fluid homeostasis, and various metabolic functions including lipolytic activity (28, 29). Low circulating NP or "natriuretic handicap" is observed in central obesity and insulin-resistant states, and lipolytic activity of atrial NP has been shown to be dramatically reduced in adipocytes of women with PCOS (28). Recently, we have shown that insulin increases the expression of NP clearance receptor C in sc adipose tissue, independent of glycemia (30). Thus, hyperinsulinemia might suppress circulating NP via up-regulation of NP clearance receptor C expression, providing a novel link between obesity, insulin resistance, and cardiovascular risk. Whether these findings can be reproduced in women with PCOS deserves further investigation.

Another theory suggests "antenatal reprogramming" as a pathogenic mechanism of insulin resistance in women with PCOS. According to this theory, reduced fetal growth and low birth weight and/or small for gestational age size followed by catch-up of weight during infancy may lead to insulin resistance and hyperinsulinemia, obesity, PCOS, and type 2 diabetes in later life. Furthermore, data from animal experiments suggest intrauterine exposure to high levels of androgen to be causatively related to defects in insulin secretion and action in adult life (31) and glucoregulatory deficits similar to those seen in adult women with PCOS (32). In animal models, the timing of the intrauterine exposure to high levels of androgen seems to have different effects on glucose regulation because early exposure appears to affect mainly the pancreatic β-cell function, whereas exposure later in gestation appears primarily to affect the insulin effectiveness. However, it needs to be determined whether this concept also applies to humans.

The androgen excess not only in the uterus but also later in life is believed to be implicated in the pathogenesis of insulin resistance in PCOS, although a cause-effect relationship is not so clear-cut (33). Recent results from our laboratory show that increased lipolysis could be causally involved in linking metabolism to circulating adrenal androgen precursors and androgen levels (34): raising serum free fatty acids and triglycerides by lipid/heparin infusion in healthy young women with regular menstrual cycles and no signs of hirsutism elevates the circulating levels of various androgens and reduces their urinary excretion (34).

In addition, there is an association between hyperandrogenemia and vascular dysfunction in PCOS (35). This may reflect the insulin resistance *per se* rather than a direct adverse effect of hyperandrogenemia (36). The hyperandrogenism favors a central/visceral distribution pattern of body fat; the latter was discussed by Kahn and Flier (37) to be a primary contributor to the development of systemic insulin resistance. Visceral fat has increased lipolytic activity and may result in relative increases of free fatty acids in PCOS (38), which in turn induce skeletal muscle insulin resistance (39). Insulin resistance is initially compensated for by hyperinsulinemia through which normal glucose tolerance is preserved. However, over time further deterioration of glucose metabolism, by increased insulin resistance or by decreased compensatory insulin secretory responses or by both, accelerates the progression to impaired glucose tolerance and eventually to overt type 2 diabetes. Chronic hyperinsulinemia *per se* exacerbates insulin resistance and contributes directly to β-cell failure and diabetes.

A role for fatty liver in the glucose abnormalities in overweight/obese women with PCOS should also be recognized (40); it is now clear that liver fat accumulation is a key feature in the pathogenesis of type 2 diabetes (41). In addition, markers of insulin resistance are associated with menstrual irregularity (42), whereas sleep apnea, which is a cardiovascular risk factor, has been found to be more

common in PCOS women and was linked to elevated fasting plasma insulin and glucose-to-insulin ratios (43).

Finally, not only insulin resistance, but also pancreatic β-cell secretory dysfunction has been reported in women with PCOS contributing to dysglycemia in this group of patients. The β-cell secretory dysfunction, indicated by hyperinsulinemia under basal conditions and a relative decrease of insulin secretion after meals, is more pronounced in PCOS women who have a first-degree relative with type 2 diabetes, and pancreatic β-cell secretory dysfunction has been demonstrated in sisters of women with PCOS compared with normal controls (44, 45).

V. Obesity

The association between obesity, in particular visceral obesity, and traditional cardiovascular risk factors is well recognized. Some 40–85% of PCOS women are overweight or obese, with elevation in BMI and waist-hip ratio, compared with age-matched controls (46). This increased prevalence of android obesity in PCOS women is particularly common (46, 47). Moreover, there is a large body of evidence that android fat distribution affects between 50 and 70% of women with PCOS, regardless of BMI (48). This excess fat, besides influencing blood pressure, lipid profile, and platelet activity, for example, contributes substantially to the increased prevalence of insulin resistance, impaired glucose tolerance, and type 2 diabetes in PCOS women (39). Put another way, weight gain in many susceptible women will lead to both the metabolic and hormonal perturbations characteristic of PCOS.

Adiposity, therefore, plays a crucial role in the development and maintenance of PCOS, and strongly influences the severity of its clinical, cardiometabolic, and endocrine features in these women. Obese women with or without PCOS have stiffer arteries than lean women. In young obese women with PCOS, central obesity rather than PCOS itself is associated with increased arterial stiffness (49). Indeed, even modest weight loss of 5% body weight results in significant improvements in symptoms (50).

Studies in women with peroxisome proliferator-activated receptor-γ gene variants, regulating lipid and energy metabolism, indicate that, in addition to severe insulin resistance, hyperinsulinemia, and features of the metabolic syndrome, these women may also present with features of PCOS; a higher frequency of C→T substitution in exon 6 of the peroxisome proliferator-activated receptor-γ gene (enhanced expression of this gene increases adipogenesis, particularly in sc adipocytes) in PCOS women has been reported that may play a role in the pathogenesis of obesity in PCOS (51), although larger studies with sufficient power will be needed to further establish these findings.

VI. Adipokines and PCOS

Further possible mechanisms for the increased incidence of traditional and nontraditional cardiovascular risk factors and metabolic disturbances, including insulin resistance, in PCOS could be related to the partly abnormal production, release, and/or function of adipocytokines and inflammatory factors. Adipose tissue has traditionally been considered an energy storage organ, but over the last decade, a novel role of the adipose tissue as an endocrine organ has emerged (52). Adipokines, such as leptin and adiponectin, and factors released by interstitial cells in adipose tissue such as TNF-α and IL may have widespread cardiometabolic effects, whereas others including vaspin (53) appear to interact with the regulation of energy homeostasis in healthy women. An alteration of these metabolic signals has been demonstrated in several studies including patients with PCOS (54).

A. Leptin

The role of leptin in PCOS is unclear, with the majority of studies having found no association with PCOS after accounting for BMI (55, 56) and no mutations of the leptin or leptin receptor genes in women with PCOS (57). However, two recent studies have noted increased leptin levels in women with PCOS independent of obesity (58, 59). Interestingly, recent data suggest that PCOS women have lower soluble leptin receptor levels, resulting in a higher free leptin index (60). Moreover, there is some evidence that regulation of leptin secretory burst mass may differ between PCOS women and normal women (61). Although these latter findings may still suggest a potential role of leptin in PCOS, any link between leptin and cardiovascular disease (CVD) risk in women remains uncertain. Furthermore, in the general population, leptin's association with CVD risk is largely dependent upon BMI (62).

B. Adiponectin

Adiponectin has antidiabetic, antiinflammatory, and antiatherosclerotic properties (63) but not necessarily linked to CVD risk. Although some studies have shown adiponectin to be lower in PCOS women (64), others have shown no difference compared with controls (64). A systematic review and a meta-analysis (65) support significantly lower adiponectin values [weighted mean difference (95% confidence interval (CI)) − 1.71 (−2.82 to −0.6); $P < 10^{-4}$] in women with PCOS compared with

non-PCOS controls after controlling for BMI-related effects, yet with significant between-study heterogeneity; low levels of adiponectin in PCOS were shown to be related to insulin resistance, but not to testosterone, and were related to PCOS severity.

Adiponectin exists in different multimeric forms, including low-molecular weight, medium-molecular weight, and high-molecular weight species. High-molecular weight adiponectin, which is a stronger predictor of insulin sensitivity (63), is lower in women with PCOS (66). Interestingly, metformin, which has been shown to impact on circulating levels of a number of adipocytokines, in a recent randomized control trial in PCOS women had no effect on adiponectin levels despite significant improvements in weight and insulin resistance (67). At present, it is fair to say that the role of adiponectin in PCOS women is still unclear.

C. Vaspin

Vaspin (visceral adipose tissue-derived serine protease inhibitor) is a novel adipokine with potential species-specific differences in its regulation and possible role(s) (68). In humans with obesity and type 2 diabetes, a positive association between vaspin gene expression in adipose tissue and serum has been demonstrated. We have shown the presence and a significant increase of vaspin in omental adipose tissue and serum in overweight PCOS women (53). The increased concentration of vaspin in the adipose tissue and plasma could be a compensatory mechanism for insulin resistance and/or glucose metabolism. However, in a large study using euglycemic hyperinsulinemic clamps, we found no association of insulin resistance with circulating vaspin, whereas vaspin was significantly elevated in women using oral contraceptives (OC) (69). Furthermore, a sexual dimorphism was detected in lean participants after exclusion of usage of contraceptives, indicating that circulating estrogen levels may influence the variance of serum vaspin levels in humans (69). In contrast, 6-month treatment with insulin improved the glycemic milieu and reduced the vaspin levels (53). Recent studies have confirmed that vaspin levels are raised in women with PCOS, but levels did not change significantly after treatment with metformin in normal-weight patients with PCOS (70). Therefore, a clear role of vaspin in the modulation of insulin resistance (or vice versa) needs to be further defined.

D. Visfatin

Visfatin is an adipocytokine preferentially expressed in visceral adipose tissue (71) with a role in obesity-associated insulin resistance and type 2 DM (72). An increase in serum visfatin levels with progressive β-cell deterioration has been observed in patients with type 2 diabetes (73), whereas studies in women with gestational diabetes had conflicting data (74, 75). Like others, we have shown increased circulating visfatin levels in women with PCOS (76–78) positively correlated with BMI (76–78), fasting plasma insulin, homeostasis model of assessment for insulin resistance (78), and blood pressure (77). Recently, metformin has been shown to significantly reduce visfatin levels in conjunction with improvement in other metabolic parameters (79). Its metabolic role in PCOS, however, still remains elusive.

E. Chemerin

Chemerin is a novel adipokine with chemotactic properties, playing a role also in adipocyte differentiation, as well as in glucose homeostasis and lipolysis in adipose tissue (80). On the other hand, obesity is considered a low-grade inflammatory state in the view of increased plasma circulating mononuclear cells and lymphocytes (81), as well as in the view of increased plasma concentration of proinflammatory cytokines (TNF-α, IL-1, IL-6), and acute phase proteins [C-reactive protein (CRP)] in this group of the population (82). Thus, chemerin could be an important part of the pathogenesis of obesity-associated insulin resistance due to its chemotactic effect. Human studies have shown a significant correlation between metabolic risk factors, blood pressure, and chemerin levels (83), whereas laboratory studies have demonstrated chemerin's insulin resistance-inducing effect in primary human skeletal muscle cells (84). We have recently shown that chemerin is increased in women with PCOS; insulin induces chemerin production, whereas metformin treatment decreases its levels (85). How medical treatments targeting chemerin will affect insulin resistance and metabolic risk in PCOS remains to be determined.

F. Acute-phase serum amyloid A (ASAA)

ASAA is a novel proinflammatory adipokine that is increased in obese, insulin-resistant subjects. Serum and adipose tissue (sc and omental) levels of ASAA are raised in women with PCOS. More recently, it has been shown that treatment with metformin for 6 months significantly reduced ASAA levels, suggesting an adipose tissue-monocyte axis involvement in pathogenesis of atherosclerosis in PCOS (86).

Collectively, these data suggest that adipose tissue dysfunction plays a central role in the metabolic abnormalities observed in women with PCOS. However, whether these abnormalities are cause or consequence to other factors observed in the syndrome, such as insulin resistance and hyperandrogenism, deserves further research.

VII. Proinflammatory and Macrophage-Derived Factors

A. Resistin

In rodents, resistin is implicated in the pathogenesis of type 2 diabetes in obesity (87) where circulating resistin levels and resistin expression in adipocytes are increased (88); however, unlike in rodents where resistin is derived from adipocytes, in humans it is produced by macrophages (89), and its precise role in humans remains controversial (90). In PCOS women, serum resistin levels were no different than matched controls (91), but resistin mRNA levels were 2-fold higher in omental adipocytes from PCOS patients; the significance of this finding remains to be defined.

B. TNF-α

TNF-α has been proposed to play a role in the pathogenesis of insulin resistance with elevated circulating levels in obese (92) and type 2 diabetic (93) subjects. In PCOS, serum TNF-α has been reported to be increased (94) irrespective of obesity, potentially implicating TNF-α in the insulin resistance of lean PCOS women. Moreover, Peral *et al.* (95) reported that a methionine 196 arginine polymorphism in exon 6 of the TNF receptor 2 gene is associated with the PCOS, although this observation needs to replicated in larger and adequately powered studies.

C. Interleukins

IL-6, a proinflammatory adipocytokine, is associated with insulin resistance and human obesity (96), and elevated levels of IL-6 may predict the development of type 2 diabetes (97). Moreover, correlations between insulin resistance and IL-6 gene polymorphism have been shown (98), as well as polymorphisms in the genes encoding IL-6 and the IL-6 signaling molecule, gp130, with the PCOS (99). However, once again, this field is still in its infancy, and there is a need for larger studies. IL-18, another proinflammatory cytokine, promotes the synthesis of IL-6 and is increased in obese women (100). IL-18 has recently been noted to be higher in women with PCOS (101). Again, the exact mechanisms involved and the potential implication for both pathophysiology and treatment options for the syndrome need to be further defined.

D. C-reactive protein and PCOS

Markers of inflammation such as CRP have been proposed to predict the risk of cardiovascular events, independent of other risk factors (102). In line with a range of elevations in various cytokines in PCOS, it is not surprising that commoner clinical measures of inflammation are in fact elevated in women with this condition (103). Boulman *et al.* (104) showed a 100% increase of CRP levels in women with PCOS, compared with BMI-matched controls. Again, it remains to be defined whether changes in inflammatory markers in women with PCOS play a causal role for the syndrome or, alternatively, are a consequence of derangements in other factors.

VIII. Gut Hormones and PCOS

It was shown that metformin could improve body weight in obese PCOS patients by acting on the central nervous system directly and indirectly via the modification of various gut hormones. In fact, it was demonstrated that metformin increases the fasting plasma levels of the anorectic gut hormone peptide YY in PCOS patients (105) and modulates appetite in the hypothalamus (106). Another study reported lower total ghrelin levels than those expected based on the presence of overweight in PCOS women, with ghrelin being negatively correlated with insulin sensitivity in obese, but not in lean, PCOS women (107). Furthermore, regardless of the presence of PCOS, a negative correlation exists between ghrelin and androstenedione levels, suggesting an interaction between ghrelin and steroid synthesis or action (107). Further complex interactions of gut hormones have been shown, partly regulated on the hypothalamic-pituitary level (108); however, many of these studies have been performed in non-PCOS subjects, and more metabolic studies in women with PCOS are needed to further elucidate the hormonal interactions specific to these patients.

IX. Dyslipidemia

Dyslipidemia is the most common metabolic abnormality in PCOS (6). Studies in PCOS women have generally reported somewhat decreased levels of the cardioprotective high-density lipoprotein (HDL) cholesterol (HDL-C) and HDL2-cholesterol, as well as elevated levels of triglycerides and very low-density lipoprotein-cholesterol levels (6). Together with commonly observed increases in triacylglycerol levels in obese women with the syndrome, the lipoprotein profile in PCOS is therefore comparable to that seen in patients with type 2 diabetes (109). A number of authors have noted comparative elevations in low-density lipoprotein (LDL) cholesterol in the PCOS population (110). Others have shown levels of small-dense LDL, known to be associated with an increased relative risk of CVD (111), to be higher in women with PCOS (112). This dyslipidemia is seen in both lean and obese women with PCOS compared with age- and BMI-matched women (113, 114). In addition, familial clustering of dyslipidemia

in PCOS women has been observed, with a probability to develop dyslipidemia being 1.8-fold higher in women with PCOS (115). In a recent retrospective study, the importance of familial dyslipidemia in PCOS was studied by comparing fasting lipids between probands and their (affected and nonaffected) sisters, where the authors suggest that body weight is the predominant influence on the manifestation of dyslipidemia in PCOS women (116). Importantly, patterns of dyslipidemia may differ among women from different ethnic groups (117), with different diets and lifestyles being contributing factors. Dyslipidemia in women with PCOS has also been shown to influence various other functions, *e.g.*, gallbladder motility (118), perhaps caused by compromised insulin suppression of free fatty acids leading to reduced levels of circulating cholecystokinin, as well as reductions in levels of incretins (119) and effects on GH levels (38), all of them with known effects on metabolism.

A relative dyslipidemia has also been found at puberty in studies on adolescent girls with a history of premature pubarche (120), and the metabolic disturbances can often be detected in the prepubertal period and throughout puberty (121). However, despite the relative consistency of these findings, it is important to appreciate that the lipid pattern in women with PCOS is only modestly more atherogenic (slight increase in cholesterol to HDL-C ratio) compared with control women with similar BMI. Furthermore, it is important to mention that despite the relatively modest changes in lipid profiles, most women with PCOS are of relatively young age and often have normal blood pressure readings, and therefore do not qualify for primary prevention of cardiovascular changes. Therefore, routine measurements of blood lipid profiles in women with PCOS may be questioned. Otherwise, because lowering of LDL to below 160 mg/dl is recommended in all subjects, irrespective of the presence of other risk factors, at least one measurement of serum lipids should be performed, and further risk factors such as smoking status and a family history of CVD should be considered for the decision whether lipid-lowering treatment should be recommended in women with PCOS.

X. Cardiovascular Dysfunction

A. Hypertension

Numerous factors affect blood pressure, including genetics, physical inactivity, stress, salt loading, etc., many of which have not been controlled for in studies that included blood pressure assessments in PCOS women. Endothelial dysfunction suggested by increased endothelin-1 levels in women with PCOS regardless of BMI (122) and higher androgen levels (probably through the renin-angiotensin system activation) (123) have been suggested as potential pathogenic mechanisms of hypertension in PCOS. Epidemiological studies, however, have shown that there is a higher prevalence of hypertension among women with PCOS, particularly systolic hypertension (124, 125). Of note, there is an increased prevalence of labile daytime hypertension (126), and over 50% of young women with PCOS fail to demonstrate the physiological nocturnal dip in blood pressure, which is a predisposing factor to sustained hypertension later in life (127). However, a retrospective cohort of women with PCOS did not confirm a higher incidence of hypertension (22). On the other hand, another study supports that at menopause, women with PCOS have a risk of developing hypertension that is 2.5-fold higher than age-matched controls, and this may be related in part to the obesity associated with PCOS (124). Whether or not rates of hypertension increase differently over time in obese women with PCOS is a difficult question to study. Taken together, there might be a predisposition of these women to hypertension in later life that may set the milieu for potential accelerated progression of atherosclerosis and cardiac dysfunction independent of their higher BMI and centripetal obesity (113), although the available evidence supporting this assumption is inconclusive.

B. Surrogate measures of atherosclerosis

PCOS women are at an increased risk of developing early-onset atherosclerosis (128). Studies have demonstrated increased carotid intima-media thickness (IMT), a predictor of coronary and cerebrovascular events, among relatively young women with PCOS (45+ yr) compared with control subjects (129). PCOS remained an independent predictor of higher IMT even after adjustment for age and BMI (35). The compliance of the common and internal carotid arteries has also been demonstrated to be decreased in young women with PCOS (128). A recent study however, didn't find any significant difference in IMT estimations between PCOS women and healthy controls (130).

Furthermore, arterial calcification correlates with the degree of atherosclerosis found on pathological examination and appears also to predict the incidence of cardiovascular events (131). In accordance with this, women with PCOS have a higher prevalence of coronary artery and aortic calcification than controls, even after accounting for BMI (132).

One study compared young (22 yr old), lean (BMI, 22 kg/m^2) PCOS women to age- and BMI-matched control women (133). The two groups were matched with regard to traditional cardiovascular risk factors, such as lipids

and blood pressure, and differed only with respect to ovulation and circulating androgens. Despite the metabolic similarity of the two groups, the PCOS women manifested greater carotid IMT, vascular dysfunction, and increased endothelin-1 compared with the control women. These results suggest the presence of both anatomic and functional abnormalities at an early age in women with PCOS that predisposes to the development of atherosclerosis.

C. Cardiac dysfunction

Cardiac systolic flow velocity is lower in PCOS women than in age-matched control women, and there is an inverse relationship between serum fasting insulin and left ventricular systolic outflow parameters; furthermore, increased insulin levels in PCOS are associated with decreased cardiac flow (134). In addition, reduced left ventricular ejection fraction and diastolic dysfunction are more common in these women (135, 136). It has also been found that normal-weight PCOS women have a significant increase in left ventricular mass index, a predictor of CVD morbidity and mortality (136). This is in accordance with the demonstrated hyperdynamic circulation (137) and increased arterial stiffness (138) in young, normotensive, nonobese women with PCOS compared with controls that indicate a mild sympathetic activation at an early age, even in the absence of classical risk factors for CVD, and may indicate an underlying cause of hypertension and cardiovascular risk.

XI. Nontraditional CVD Risk Factors

The coexistence of hypertension, hyperlipidemia, and impaired glucose tolerance (IGT) appears to account for only part of the observed excess risk for CVD in insulin-resistance states; some of the other risk may be attributed to the insulin resistance-related impaired nitric oxide generation by the endothelial cells, the hyperinsulinemia-induced impaired fibrinolysis, and the hyperglycemia-activated coagulation (139). All these abnormalities are parameters of the so-called endothelial dysfunction that follows states of severe insulin resistance like PCOS.

It has been shown that young women with PCOS who are free of any cardiovascular risk factors including obesity, dyslipidemia, and hypertension had altered endothelial function, as it was assessed by flow-mediated dilation of brachial arteries, IMT at carotid artery, and serum endothelin-1 values when compared with age- and BMI-matched healthy subjects, suggesting early functional, structural, and biochemical preatherosclerotic vascular impairment (133). Other parameters associated with cardiovascular risk factors shown to be abnormal in PCOS when compared with matched controls include elevated plasma activator inhibitor-1 (PAI-1) activity (133), hyperuricemia (46), elevated endothelin-1 (133), vascular endothelial growth factor (140), highly sensitive CRP (141), and low tissue plasminogen activator (142). Interestingly, tissue plasminogen activator and PAI-1 do not seem to be correlated with indices of insulin resistance or androgens, although there are few studies showing that treatment with metformin lowers PAI-1 in PCOS women, just as it does in type 2 diabetes (142). The data on endothelial dysfunction, ascertained by a variety of differing methods, in PCOS is inconsistent (143). However, how these factors may account for the potential increased cardiovascular morbidity associated with PCOS remains unclear.

Another important risk factor is represented by asymmetric dimethylarginine (ADMA), a guanidine-substituted analog of L-arginine, which is a potent endogenous competitive inhibitor of the endothelial nitric oxide synthase. Increased levels of ADMA reduce NO formation and are associated with endothelial dysfunction (144) and atherosclerosis and are correlated with traditional cardiovascular risk factors, representing an independent marker for cardiovascular morbidity and mortality (144–147). We have recently demonstrated that ADMA is increased in women with PCOS when compared with controls and decreased significantly after metformin therapy, with fasting insulin being the most important predictor of ADMA levels (148); compatible with our findings are the results of subsequent studies (149, 150). A recent study, however, did not find any significant difference in ADMA levels between PCOS women and healthy controls (130).

Regarding cardiovascular risk factors in PCOS, it was recently demonstrated that PCOS women show abnormal (slower) heart rate recovery when compared with healthy controls (151). The latter has been related to increased risk for cardiovascular mortality (152) and was shown to be closely associated with increased inflammatory markers in PCOS women, acting probably in concert to increase the cardiovascular risk profile of these patients (153). Finally, the lipid accumulation product index (113) and the presence of pre-microalbuminuria (albumin creatinine ratio $\gg$7 mg/g) in women with PCOS (154) were suggested as useful markers of cardiovascular risk assessment in women with PCOS. Table 1 summarizes the studies that provide the best evidence for CVD and type 2 diabetes in women with PCOS, whereas Table 2 summarizes the incidence of the well-established (lipids, blood pressure) and more novel (*e.g.*, vascular function, inflammation markers, hemostatic factors, and adipokines) risk factors for CVD and diabetes in PCOS, plus the strength of evidence to link each to PCOS with +, ++, or +/− signs.

TABLE 1. Studies that provide best evidence regarding incidence of CVD and type 2 DM in women with PCOS

	Design of the study	No. of PCOS women	Findings	Refs.
Best evidence for CVD risk	31-yr follow-up study of women diagnosed with PCOS	786	No significant increased risk of death from cardiovascular-related causes	219
	Retrospective cohort study	319	Excess of nonfatal cerebrovascular events	22
	14-yr prospective cohort of female nurses with irregular menses (PCOS not confirmed)	82,439	50% increased risk for nonfatal or fatal CVD compared to age- and BMI-matched women without PCOS	42
	Postmenopausal women with or without premenopausal history of irregular menses	390	More angiographic coronary artery disease ($P = 0.04$); lower cumulative 5-yr cardiovascular event-free survival (78.9 *vs.* 88.7%; $P = 0.006$)	221
	Mothers of women with PCOS		After adjustments for age and race, PCOS was shown to be an independent predictor of cardiovascular events (odds ratio, 5.41; 95% CI, 1.78 to 16.40)	223
Best evidence for DM risk	Prospective study of PCOS women	254	7.5% had diabetes	17
	Multicenter clinical trial	394	6.6%	18

XII. PCOS and Nonalcoholic Fatty Liver Disease (NAFLD)

NAFLD is an increasingly recognized chronic liver disease in which excess fat accumulates ectopically in the liver of individuals with minimal alcohol consumption. Reports estimate its prevalence rates between 25 and 33% in the United States (155) and 20 and 30% in Europe (156). Its natural history is not always benign because fatty liver can potentially progress to nonalcoholic steatosis hepatitis (NASH) (inflammation and hepatocellular necrosis) (157), cirrhosis, or even hepatocellular carcinoma (158, 159). Another reason that makes NAFLD an important clinical condition is that intrahepatic lipid content and disturbed glucose metabolism are linked by a complex network of signaling factors (160), and thus may predict the development of diabetes (161), atherosclerosis, and CVD (161).

The majority of patients with NAFLD are asymptomatic, and the diagnosis is suspected after finding elevated transaminases on routine testing (162). However, more than two thirds of patients with any histological spectrum of NAFLD may be missed if the diagnosis just relies upon aminotransferase levels (163, 164), although several indices have been proposed recently for the prediction of NAFLD, including states of advanced fibrosis that appear to perform more favorably (165, 166). Nevertheless, liver biopsy remains the "gold standard" for distinguishing between simple steatosis and NASH and for disease severity assessment, although recent noninvasive assessments of NAFLD severity including risk scores, biomarker panels, and sonographic measurements promise much improved screening for at-risk patients and for follow-up of treated or untreated patients, without recourse to the use of liver biopsy on a routine basis (167–169). Future trials should optimize the noninvasive diagnostic strategies.

Obesity and insulin resistance are considered key features of NAFLD (170). Insulin resistance in particular is considered pivotal in the pathogenesis of NAFLD, irrespective of obesity (35), via the excessive free fatty acid flux from the adipose tissue to the liver and the hyperinsulinemia-promoted hepatic *de novo* lipogenesis (172). The extent of steatosis is related to the degree of insulin resistance (173), whereas the fatty liver is itself insulin resistant, making obvious the close interlinks between the two entities. More importantly, insulin resistance represents the main predictor for the progression from simple steatosis to NASH that carries the risk of progressive liver injury and death. On the basis of insulin resistance and obesity, women with PCOS are expected to demonstrate a high prevalence of NAFLD. This has been confirmed by several studies (174–178), which suggests a significantly higher prevalence of NAFLD in PCOS women (27.4–62%) (177, 179) compared with weight- and age-matched non-PCOS females (180), although from the description of the cohort, it cannot be excluded that all patients with PCOS were identified/excluded in the latter study, which might have led to a more pronounced difference between groups. The opposite is also true (high prevalence of PCOS in female patients of reproductive age who suffer from NAFLD) (179, 181), suggesting a close link between the two conditions. Although several single components of the metabolic syndrome including low HDL-C levels, hyper-

TABLE 2. Incidence of well-established and novel risk factors for CVD and diabetes in PCOS

Risk factors for CVD and diabetes in PCOS	Incidence/ concentration in PCOS	Strength of evidence	Refs.
Dyslipidemia	Increased	++	6, 22, 38, 110, 112, 113, 282–288
Hypertension	Increased	+/−	22, 112, 113, 124, 283
Insulin resistance	Increased	++	9, 13, 17, 18, 289, 290
Pancreatic β-cell secretory dysfunction	Increased	++	44, 45
Obesity	Increased	++	14, 18, 37, 46, 47, 289, 290
NAFLD	Increased	++	40, 185, 196
Adipokines and macrophage derived factors			
Adiponectin	Reduced	+	65
Resistin	Increased	+/−	91
Vaspin	Increased	+	53
Visfatin	Increased	+	76–78
Chemerin	Increased	+	85
Inflammation markers			
TNF-α	Increased	++	94, 95
IL-6	Increased	++	99, 291
IL-18	Increased	+	101
CRP	Increased	++	103, 141
Endothelial/vascular function			
Endothelial/vascular dysfunction	Increased	++	35, 36, 122, 133, 139, 292–301
Plasma PAI-1 activity	Increased	++	302–304
Endothelin-1	Increased	++	133
Vascular endothelial growth factor	Increased	++	305
ADMA	Increased	++	148–150
Carotid IMT	Increased	++	35, 129, 306, 307
Coronary artery and aortic calcification	Increased	++	132, 307
Left ventricular mass index	Increased	++	132, 136, 307
Tissue plasminogen activator	Increased	++	142
Heart rate recovery	Slower	++	151, 153

Strength of evidence to link each to PCOS is shown with +, ++, or +/− signs.

triglyceridemia, high BMI (176), hypertension (169), estrogens (179), and hyperandrogenemia (40, 182) have been considered important determining factors accounting for NAFLD in PCOS, multivariate regression models revealed that insulin resistance is the only independent contributor to NAFLD in PCOS and has a key role in liver disease progression (169, 173–177, 183). This is also suggested by studies in adolescents with PCOS (184) and lean PCOS women (175). However, in contrast to what happens in other population subgroups where only a minority of patients who suffer from NAFLD progress to NASH (180), the prevalence of advanced liver disease (NASH with fibrosis) in women with PCOS is remarkably high (181, 185), even in the adolescent females with PCOS (186). This is a very important finding considering that NASH carries the risk of progressive liver injury and cirrhosis as well as the development of diabetes (161), atherosclerosis, and CVD (187, 188).

The therapeutic interventions target visceral adiposity (if excessive) and insulin resistance that are critical in the pathogenesis of NAFLD/NASH and should prevent or reverse hepatic cellular damage (intrahepatic inflammation and necrosis) induced by liver fat content and subsequent lipotoxicity. At present, no medication is licensed to treat NAFLD. Therefore, current advice is that patients should lose weight and be screened for cardiovascular risk factors and appropriately treated. Weight loss of only 5–10% of initial body weight should be implemented as first-line therapy in all patients with NAFLD/NASH (189, 190) and is usually enough to reduce steatosis and improve liver function tests (191). However, weight loss alone is not enough to reverse fibrosis (192). Thus, in more advanced cases of liver disease (NASH with fibrosis), additional pharmacological therapy directed at the correction of insulin resistance (insulin-sensitizing agents) and concurrent metabolic disorders (statins, antihypertensive agents, etc.) should be given as needed, whereas specific hepatoprotectors such as antioxidants and antiinflammatory agents (193) may also have a role in the therapeutic strategy.

Weight loss also seems crucial in the conversion of the natural history of NAFLD in obese PCOS women (194). Remarkably, there is increasing evidence that weight loss induced by bariatric procedures could be beneficial for patients with more advanced liver disease (NASH) (195). Metformin is an insulin sensitizer that also has beneficial effects on liver function tests and liver histology in obese PCOS women with NAFLD (196). Similarly, omega-3 fatty acid supplementation has been shown to reduce liver

fat content in women with PCOS (197), probably via activation of peroxisome proliferator-activated receptor-α. Glitazones represent another group of insulin sensitizers that have consistently shown some benefit in patients with NASH (198). None of these interventions, however, have shown convincing evidence on reversing fibrosis. In addition, whether improvement of the liver function tests does also suggest reduction in cardiometabolic events warrants further study.

In conclusion, NAFLD is frequently seen in patients with PCOS, and this does not exclude adolescents with the disorder. In addition, PCOS has been related to more frequent and advanced forms of liver disease (NASH), perhaps related to the observed more severe insulin resistance in these patients. Therefore, women with PCOS should be screened for NAFLD at an earlier age, particularly those with evidence of metabolic syndrome, and treated properly. Weight loss of at least 5–10%, as well as treatment with metformin or insulin sensitizing drugs are currently suggested as the most appropriate initial therapeutic interventions in PCOS patients with NAFLD, along with screening and appropriate management of cardiovascular risk factors. Further studies are needed to define the set of tests to be carried out in patients with PCOS and NAFLD (liver biopsy or noninvasive markers of fibrosis) as well as the optimal therapeutic strategy for NAFLD/NASH in this subgroup of the female population.

XIII. PCOS and Obstructive Sleep Apnea (OSA) Syndrome

OSA is a condition of recurrent collapse of the upper airway during sleep, resulting in reductions in oxygen saturation and transient arousal, typically not remembered by the individual. Obesity (particularly central), increased age, male sex, and the phenotype of enlarged tongue, soft palate, uvula, and tonsils, with increased neck circumference reducing the upper-airway cross-sectional area, are considered the main predisposing factors for OSA development (199), whereas alcohol, sedatives, and antihistamines may increase the frequency and severity of OSA episodes. The condition may be completely asymptomatic or may be associated with a variety of nocturnal symptoms including snoring, choking, restlessness, or even nocturia (because of the recurrent arousal). The diagnosis is established by a sleep study in which the number of the apnea/hypopnea episodes occurring hourly during sleep is estimated. According to the results, OSA is classified as mild, moderate, and severe when the number of episodes ranges between five and 14, 14 and 29, and greater than 30, respectively; less than five episodes per hour is normal.

There is evidence that OSA is related to metabolic disturbances including insulin resistance and diabetes (200) independently of the degree of obesity (201), and is a well-recognized risk factor for CVD (202, 203) and atrial fibrillation (204). It is suggested that both poor quality (fragmentation) of sleep and the intermittent hypoxemia caused by OSA may lead to increased sympathetic activity and activation of the hypothalamic-pituitary-adrenal axis, with subsequent elaboration of cortisol and proinflammatory cytokines in blood that increase the free fatty acid flux to the bloodstream, leading to adverse consequences to glucose metabolism (205). In addition, it has been demonstrated that sleep deprivation may alter appetite regulation, reducing levels of leptin increasing ghrelin, and leading to increased appetite, with increases in preference for carbohydrates (206). The observed weight gain in the intensive treatment group of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study may be related to unrecognized development of OSA, thereby potentially contributing to the increased mortality in this group (207). Furthermore, the OSA-associated sympathetic nervous system hyperactivity, hyperinsulinemia, and hypercortisolemia also activate the renin-angiotensin-aldosterone system and cause hypertension (208). Finally, OSA is considered an independent risk factor of endothelial dysfunction (209); the OSA-associated oxidative stress, subclinical inflammatory state, and hypercortisolemia may be the underlying causes for this effect. Thus, OSA is causatively linked to atherogenic metabolic milieu and puts patients at increased risk for CVD. On the other hand, treatment of OSA ameliorates the cardiovascular risk factors including glycemia (201, 210). The treatment of OSA used currently is continuous positive airway pressure (CPAP) that prevents upper airway collapse and oral appliances to bring the jaw forward; occasionally, surgical correction of anatomic defects that narrow the upper respiratory tract may reverse the apneic/hypopneic episodes.

In previous reports, the prevalence of OSA in women with PCOS (even in premenopausal subjects) (43) exceeded that observed in women without PCOS after adjustment for age and BMI and was 5- to 30-fold higher (43, 211). Because sex steroids have been proposed to play a role in the pathogenesis of OSA, one possibility for the high prevalence of OSA in PCOS could be androgen excess (211, 212); other studies, however, failed to show any significant relationship between androgen levels and severity of OSA in PCOS (43, 213), suggesting that factors other than the androgen excess may be involved in the increased prevalence of OSA in PCOS. The low proges-

terone theory provided another potential pathogenic mechanism, according to which the differences in sleep measures that exist across the normal menstrual cycle may be due to altered progesterone concentration. In particular, it has been estimated that the upper airway resistance is lower during the luteal phase when progesterone is higher compared with follicular phase when progesterone is low (214), and the same thing happens during pregnancy in which the severity of preexisting OSA is markedly attenuated at the same time that progesterone levels markedly increase (215). Progesterone is thought to promote its effects through direct stimulation of respiratory drive (216) and enhancement of the upper airway dilator muscle activity (217) by which it reduces airway resistance. Because women with PCOS have usually anovulatory cycles, and thus circulating progesterone concentrations reflecting the constantly lower levels of the follicular phase, this may contribute to the high prevalence of OSA in this disorder.

OSA provides an important and perhaps a key determinant of insulin resistance and glucose intolerance in women with PCOS, independent of BMI (43, 218), whereas the severity of OSA might determine the severity of insulin resistance and accelerate the conversion from normal to impaired glucose tolerance (213). Indeed, the prevalence of IGT is approximately 2-fold higher (55 *vs.* 23%) in women with PCOS who have OSA compared with those without OSA, whereas successful treatment of OSA improves cardiometabolic function, blood pressure, and insulin sensitivity in young, obese women with PCOS, independently of concurrent changes in body weight (218). These findings suggest that should OSA be successfully managed, this may benefit young PCOS women who face a lifelong risk of CVD and type 2 diabetes.

A recent study showed that 8-wk home treatment with CPAP modestly improved insulin sensitivity independent of BMI in women with PCOS and OSA. Daytime diastolic blood pressure decreased by 2.3 mm Hg after CPAP, accompanied by reductions in norepinephrine levels. The magnitude of these effects was modulated by hours of CPAP use and degree of obesity. The optimal use of CPAP for cardiovascular and metabolic improvement is yet to be determined (218).

In summary, women with PCOS suffer from sleep disorders including OSA much more often than females without PCOS. Data from several studies suggest a causative link between OSA and insulin resistance in PCOS, whereas effective OSA treatment seems to improve the adverse metabolic milieu. Considering that OSA is associated with high risk of diabetes development and CVD, clinicians who manage PCOS patients should be aware of the high prevalence of OSA in these patients and systematically screen these women for OSA (polysomnogram).

XIV. Vascular End-Point Data in PCOS

Given that many risk factors are perturbed in women with PCOS and that vascular risk is elevated (Table 1), to what extent does this translate into more frequent or earlier events, thereby providing a rationale if any for screening? The definitive answer is unfortunately lacking because there have been no adequately powered prospective epidemiological studies with the requisite baseline phenotyping. However, analysis of the contribution from the relative components of the diagnosis of PCOS is helpful in this respect. In a long-term follow-up study of 786 women diagnosed with PCOS, primarily based on ovarian wedge resection histopathology, there was no significant increased risk of death from cardiovascular-related causes after an average follow-up of 30 yr (219). Although this finding was confirmed in a subsequent study of a subgroup of 319 women with better-defined PCOS (22), an excess of nonfatal cerebrovascular events (PCOS, 13 of 319; controls, 10 of 1060) despite adjustment for BMI was evident (odds ratio, 3.4; 95% CI, 1.2–9.6). Similarly, with respect to hyperandrogenism *per se*, the association with CVD in women is weak. So far, the most convincing studies suggesting increased CVD risk in PCOS comes from a study by Solomon *et al.* (220) and Shaw *et al.* (221). In a prospective cohort of 82,439 female nurses, Solomon *et al.* (220) linked history of prior menstrual regularity (at ages 20–35 yr) in 1982 to subsequent CVD end-points over 14 yr of follow-up. There were 1417 incident cases of CVD. Compared with women reporting a history of very regular menstrual cycles, women reporting usually irregular or very irregular cycles had an increased risk for nonfatal or fatal CVD [age-adjusted relative risk, 1.25; 95% CI, 1.07–1.47; and relative risk, 1.67; 95% CI, 1.35–2.06, respectively]. Importantly, the increased risk for CVD associated with very irregular cycle group remained significant (RR, 1.53; 95% CI, 1.24–1.90) after adjustment for BMI and several potential confounders inclusive of age, smoking, parity, and menopausal status. However, adjusting for further factors such as diabetes, hypercholesterolemia, or history of hypertension attenuated the risk, indicating that traditional risk factors do at least in part account for the increased risk of cardiovascular events in women with PCOS. Otherwise, in the first long-term prospective follow-up study, Schmidt *et al.* (222) did not find an evident increase in cardiovascular events in women with PCOS *vs.* controls during the postmenopausal period, despite higher rates of hypertension and hypertriglyceridemia in the

PCOS group. Although the relatively small size of this study (25 women with PCOS and 68 controls that participated in all examinations) may not allow the detection of potentially present smaller differences in morbidity and mortality rates between groups, the results were in agreement with findings from others pointing at a potential protective combination of hormonal and other factors in women with PCOS that may protect from the expected higher rates of cardiovascular events in these patients (22, 23).

Although chronic anovulation and cycle irregularity can be heterogeneous in origin, approximately 80–90% of women with very irregular cycles are likely to have PCOS. Accounting for this, the data suggest that PCOS is associated with approximately a 50% increased risk for CVD compared with age- and BMI-matched women without PCOS. More recently, Shaw *et al.* (221) evaluated the risk of cardiovascular events in 390 postmenopausal women enrolled in the NIH-National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Of the 390 women enrolled, a total of 104 women had PCOS defined by clinical features: a premenopausal history of irregular menses and current biochemical evidence of hyperandrogenemia. Interestingly, the authors reported that women with clinical features of PCOS had more angiographic coronary artery disease ($P = 0.04$) compared with women (n = 286) without clinical features of PCOS. More importantly, the cumulative 5-yr cardiovascular event-free survival was 78.9% for women with PCOS *vs.* 88.7% for women without clinical features of PCOS ($P = 0.006$). The 2-fold increase in cardiac events in the PCOS women in this study is similar to the 2-fold increased risk of a fatal myocardial infarction in PCOS women reported by the Solomon *et al.* (220) study reviewed earlier. In addition, the average age of the women in the WISE study was 63 yr, and the cardiovascular event-free survival curves diverged immediately from entry into the study, suggesting that cardiovascular events may occur at an earlier age in PCOS women compared with normal women. Finally, although women with PCOS had a greater clustering of metabolic risk factors, PCOS remained a significant predictor ($P < 0.01$) in prognostic models including hypertension, waist circumference, diabetes, and angiographic coronary artery disease as covariates.

Trying to overcome the lack of definitive diagnosis of PCOS in an older population, a recent study assessed mothers of women with PCOS (223). It took advantage of the high heritability of PCOS and determined the probable PCOS status and the risk of cardiovascular events of the mothers of women with PCOS population. After adjustments for age and race, PCOS was shown to be an independent predictor of cardiovascular events (odds ratio, 5.41; 95% CI, 1.78 to 16.40); more interestingly, the adverse cardiovascular events occurred at an earlier than expected age in mothers with PCOS. Although the latter odds ratio appears high, the small number of events means a wide confidence interval. Perhaps the best quality data remains those from the Nurses Health Study alluded to above. Putting it all together, the "absolute" risk for vascular events in the majority of women with PCOS will remain relatively low due to both young age and female gender. This point cannot be overemphasized because absolute rather than relative risks must influence clinical decision-making.

The recent consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society recommends BMI, waist circumference, serum lipid/glucose, and blood pressure determinations for all women with PCOS, as is oral glucose tolerance testing recommended in those with obesity, advanced age, personal history of gestational diabetes, or family history of type 2 DM. Lifestyle management is recommended for primary CVD prevention, targeting LDL and non-HDL-C and adding insulin-sensitizing and other drugs if dyslipidemia or other risk factors persist (224).

XV. Management

The association of PCOS with features of the metabolic syndrome, including insulin resistance, obesity, and the increased risk of developing type 2 diabetes, along with increased cardiovascular risk factors, no doubt has a number of important clinical implications. What is not appreciated is the fact that PCOS is a general health problem, and not an issue only involved in infertility or menstrual disturbance. We suggest that the global management of PCOS should consider the metabolic and vascular risk aspects. However, such management should consider cost effectiveness of any screening method and also whether management would be significantly altered. Before we give specific recommendations, it is useful to review the effects of differing interventions on cardiovascular and diabetes risk factors in women with PCOS.

A. Lifestyle modifications

With increased risk of developing abnormal glucose homeostasis and type 2 diabetes, the prevention of these metabolic complications is of key significance. Weight loss, in particular a decrease in abdominal fat, or prevention of further weight gain is therefore an important management strategy. Indeed, the benefits of weight loss on both clinical and biochemical manifestations in PCOS

women have been previously documented (225). Besides improvements in menstrual cycles, fertility, and hirsutism, weight loss intervention studies have noted a decrease in insulin resistance, lower serum insulin levels, improved lipid profiles, and also a decrease in abdominal fat. Indeed, from the literature on the subject of diabetes, it has been shown that changes in diet and exercise habits can delay the onset of diabetes (226). In these studies, the diet was high in cereal fiber and polyunsaturated fat, low in saturated fats, and low in glycemic load, and exercise was taken regularly. Therefore, weight loss through lifestyle measures should be indicated as a primary treatment for many obese women with PCOS. In the diabetes prevention program lifestyle intervention, a low-fat diet and 150 min of exercise per week, compared with metformin therapy 850 mg twice daily, showed that at the end of the 3-yr period of follow-up, lifestyle intervention reduced the risk of developing diabetes by 58%, whereas metformin reduced the risk by 31% (227). Recently, the results of the 10-yr follow-up of the Diabetes Prevention Program trial were published, according to which the benefits of lifestyle intervention and metformin treatment for preventing the development of diabetes in high-risk adults can persist for 10 yr. It was reported that the overall diabetes incidence was reduced by 34% in the lifestyle group and by 18% in the metformin group, relative to placebo (228).

Current lifestyle recommendations, in terms of dietary composition, propose a high carbohydrate, moderate protein, and low fat intake (229). More recently, however, interest has shifted to increasing dietary protein and decreasing carbohydrate intake, where it has been suggested that such dietary composition aids in increased weight loss and improves insulin sensitivity (230). However, despite short-term weight loss through exercise and dietary composition, sustained long-term weight loss in women with PCOS is disappointing. As in individuals who are overweight and obese but do not have PCOS, there are other factors beside diet modification and physical activities that may lead to a poor response in terms of sustained weight loss. For example, in subjects with PCOS, one needs a better understanding of the psychological background in these women given the observation that women with PCOS have higher levels of stress and also a negative self-image (168). Therefore, behavior modification and reduction of stress are also important in lifestyle modifications.

In a recent randomized controlled trial involving overweight and obese clomiphene citrate-resistant women with PCOS, the probability of ovulation was increased significantly by structured exercise and a hypocaloric diet (231). There are only a few randomized controlled trials involving lifestyle interventions in women with PCOS. There is evidence that lifestyle changes improved body composition, hyperandrogenism, and insulin resistance. There is no evidence of effect for lifestyle intervention on improving glucose tolerance or lipid profiles and no literature assessing clinical reproductive outcomes, quality of life, and treatment satisfaction (19). Clearly, women with PCOS have more to gain from losing weight or preventing further weight gain, but additional studies are needed to understand how best to achieve this in women with this challenging condition.

Recently, it has been shown that women with PCOS have impaired cardiopulmonary functional capacity (232). Vigorito *et al.* (233) investigated the effects of a 3-month exercise-training program on cardiopulmonary functional capacity in young PCOS women. Compared with women who did not undergo a 3-month structured exercise training program, those women who trained showed a significant improvement in peak oxygen consumption had maximum workload. Moreover, there was significant reduction in BMI with significant improvement in insulin sensitivity, but also a decrease in the inflammatory marker CRP. It should be emphasized that exercise improves insulin sensitivity by not only assisting in weight management but also by directly affecting muscle metabolism (234). Furthermore, it is important to recognize that significant benefits can be gained through an exercise program with only modest changes in energy expenditure or weight reduction (235). Indeed, a recent Cochrane review showed that whereas weight loss was achievable by exercise intervention alone, the overall effect was modest, although effects on risk factors were present even with minimal weight loss. A recent study also showed significant improvement in several components of the lipoprotein profiles of women with PCOS after a moderate-intensity exercise program without weight loss (236), supporting the importance of physical activity in addressing insulin resistance and associated metabolic disturbances in this high-risk population. A structured exercise program was also shown to improve compliance and subsequently fertility in obese PCOS patients with anovulatory infertility more than diet alone (237).

Therefore, although exercise or increased activity may not result in substantial change in body weight, it should be emphasized as a routine and integral component of lifestyle intervention in such women. However, in our experience, we have found that lifestyle intervention produces positive results only in highly motivated individuals who show a willingness to change. Hence, lifestyle intervention through both diet and exercise produces limited results and in essence is usually combined with pharmacological therapy.

B. Pharmacotherapy

It should be appreciated that PCOS is characterized by chronic anovulation, hyperandrogenism with clinical manifestations of irregular menstrual cycles, subfertility, hirsutism, and acne. Hence, in clinical practice, although one would focus on the metabolic and cardiac manifestations of PCOS, treatment is usually tailored to symptoms. However, certain treatments aimed at improving these symptoms may have detrimental effects on other components of the syndrome, particularly the cardiometabolic aspects.

We therefore briefly describe different treatment options for women with PCOS with more of a focus on the cardiometabolic angle.

1. OC pill (OCP)

OC have been the mainstay of PCOS pharmacological therapy for decades. When compared with any other therapy, such as insulin sensitizers and insulin-lowering agents, OC are more effective in improving menstrual pattern and reducing serum androgen levels. Although some studies report unfavorable metabolic effects such as worsening of insulin resistance in individuals using certain OC (238), meta-analyses do not support worsening of metabolic profiles with OC use in general, and differences in study outcomes may depend on the specific progestin used. Current evidence suggests that OC have limited effect on carbohydrate metabolism in women without diabetes (239). Dyslipidemia in patients using OC has been mainly linked to the progestogen component of OC (240). Although some of the OC appear to significantly raise HDL levels (240, 241), the size of the effect was generally small, and there is relevant heterogeneity between investigated cohorts (240). Furthermore, potential beneficial cardiovascular effects of OC use have not been proven and may, among other factors related to the treatment, depend on specific OC-induced changes in HDL composition.

Furthermore, usage of OC may interfere with various hormonal and metabolic signals, *e.g.*, serum vaspin (69). Notably triglycerides, fat mass, and abdominal fat mass have been reported to increase along with IL-6, whereas the antiinflammatory and antiatherogenic adipokine, adiponectin, has been reported to be decreased (242). The use of the OCP and its associated adverse effects on metabolic parameters is particularly relevant in the obese patient with PCOS. In a very recent randomized, controlled, 6-month study (238) using the OC (35 mg ethinyl estradiol/2 mg cyproterone acetate), the most commonly prescribed OC, showed that the OC increased insulin resistance by 25% (as measured by area under the curve on oral glucose tolerance test). More importantly, this increased insulin resistance was associated with an increase in arterial stiffness, a predictor of cardiovascular risk, highlighting the importance of tailored treatment of medical therapy in PCOS women, especially the obese group (238). Of interest, however, in the same study, a low dose of the OC (20 μg ethinyl estradiol/100 μg levonorgestrel combined with spironolactone 50 mg twice a day) revealed a neutral effect on insulin resistance and did not worsen arterial stiffness as measured by a pulse wave velocity. Hence, a low estrogen preparation may be preferable if contraception is required, and a combination with an antiandrogen with known blood pressure effects, such as spironolactone, seems to be tolerable.

The use of antiandrogen therapy varies globally. Cyproterone acetate that is commonly used in Europe, in high doses has been shown to worsen triglyceride levels and is associated with venous thrombosis (243). On the other hand, spironolactone that is commonly used in the United States, when combined with lifestyle changes, in particular in the obese PCOS group, decreased insulin resistance and hyperinsulinemia (244).

Finally, flutamide—a nonsteroidal antiandrogen—has been shown to improve lipid profiles and adipokine levels (242). More recently, Gambineri *et al.* (245) have reported a decrease in visceral fat content and an improvement in insulin sensitivity, with reduction in LDL cholesterol levels in women with PCOS taking flutamide. These findings are of interest, particularly given that cardiovascular risk in PCOS is associated with insulin resistance, obesity, and hyperandrogenemia. Therefore, along with lifestyle measures, in the treatment of dieting overweight-obese PCOS women, there seems a rationale for targeting different therapeutic options according to the required outcomes in the long term. That noted, few of the above medications have been tested in long-term trials or with attention to clinical end-points.

2. Insulin sensitizers and insulin-lowering agents

There is a general consensus that insulin resistance and, in particular, hyperinsulinemia leads to hyperandrogenemia and is associated with cardiovascular risk factors. The most extensively studied insulin-lowering drug in the treatment of PCOS is metformin. A recent systematic meta-analysis based on modest numbers, comparing metformin with either placebo or no treatment, demonstrated that metformin reduced blood pressure, fasting glucose, and serum androgens with no effect on body weight or hirsutism scores (246). However, other studies have concluded that metformin lowers BMI in women with PCOS, in line with data in the general population or those at risk of diabetes (247).

Furthermore, usage of metformin was associated with significant reduction of waist circumference and visceral

adiposity compared with weight loss by lifestyle modifications only (106, 248–250). Maybe higher doses need to be used with increasing adiposity for weight loss effect of metformin to occur (251).

There are a number of studies that have shown that metformin improves metabolic parameters in PCOS women. Not only in the adult PCOS women but also in the severely insulin-resistant adolescent with PCOS and IGT, metformin therapy has been reported to normalize glucose tolerance in half of these subjects, lower total and free testosterone, decrease BMI and sc adipose tissue, and improve insulin sensitivity (252, 253). The effect of metformin on improving insulin sensitivity in women with PCOS does not seem to be dose-dependent (254).

However, although initial studies would have suggested that metformin may be the treatment of choice for anovulation in PCOS, it is now suggested that metformin may be least effective in those who are extremely obese (BMI greater than 35 kg/m^2) (255). The issue of whether clomiphene or metformin should be first-line treatment in PCOS women desiring pregnancy is controversial (256, 257) and depends in part on the age and desires of the patient as well as the time line. Clomiphene is superior to metformin in achieving live birth in infertile women with the PCOS (258), and there is no evidence that a combination of metformin and clomiphene is superior to either of the drugs alone (259). Furthermore, as a practical point, it should be appreciated that normalization of ovulation will increase fertility, a possible unwanted effect in the adolescent population in particular. Hence, careful counseling must be provided to the adolescent PCOS subject, and it may be necessary to add a low dose of OCP to prevent pregnancy. There is conflicting evidence about whether metformin treatment during pregnancy for women with PCOS improves maternal and fetal outcomes (260, 261).

Finally, the most recent Cochrane Systematic Review analyzing insulin-sensitizing drugs *vs.* the combined OCP, in PCOS subjects, concluded that metformin was more effective than the OCP in reducing fasting insulin and triglycerides, but there was insufficient evidence regarding comparative effects on reducing fasting glucose for cholesterol levels (262). Moreover, the OCP showed that it was associated with an improved menstrual pattern and serum androgen levels compared with metformin. More importantly, the authors concluded that there was either extremely limited or no data on important clinical outcomes such as developmental diabetes, CVD, or indeed endometrial cancer. The review indicated that there were no trials comparing metformin *vs.* the OCP in terms of cardiovascular outcomes, including stroke and myocardial infarction, and that there was only one trial that compared metformin *vs.* the OCP in relation to the development of type 2 diabetes, where no difference was seen between the two groups; there was also no difference in BMI between the metformin and OCP treatment groups, or indeed waist/hip ratio (262). However, a recent retrospective study of PCOS women had different findings. According to the investigators, metformin treatment for an average of 43 months delayed or even prevented the development of IGT and type 2 diabetes; in fact, there was an 11-fold decrease in the annual conversion rate from normal glucose tolerance to IGT, with 55% of IGT patients reverting to normal glucose tolerance (263). In accordance with these findings are the results of a meta-analysis by Salpeter *et al.* (264) that included 14 trials with PCOS subjects and demonstrated a decrease by 40% of new-onset DM and a reduction by 6% in the absolute risk of DM by the use of metformin, as well as the results of the 10-yr follow-up of the Diabetes Prevention Program trial (228).

A recent randomized open-label study explored whether metformin prevents adolescent PCOS in girls with a history of low birth weight and precocious pubarche who are prone to develop this condition. Thirty-eight girls were followed up from mean age of 8 until 15 yr and were treated with metformin early (ages 8–12) or late (ages 13–14). Hirsutism, oligomenorrhea, and androgen excess were two to eight times higher in the late-treated girls (265).

Metformin was also shown to have a better profile than placebo (266, 267) and antiandrogenic OC (268) regarding blood pressure in women with PCOS. Furthermore, it may improve endothelial structure and function and reduce IMT in PCOS women (269) and might have a beneficial effect in cases of atypical endometrial hyperplasia (270). It should be noticed, however, that metformin does not maintain its benefits at the biochemical and clinical level after treatment suspension, whereas a slight but significant worsening of the basal peripheral insulin sensitivity might be seen after treatment cessation (271). However, it needs to be noted that very few large randomized controlled trials exist in the literature supporting the efficacy of metformin in the treatment of PCOS, and those that exist show only moderate advantages of treatment with metformin in comparison with other treatments (258).

Table 3 summarizes some of the reported effects of metformin in PCOS.

3. Antiobesity agents

Orlistat, a pancreatic lipase inhibitor, limits the absorption of dietary fat, and we have recently shown that it significantly reduces body weight and total testosterone

TABLE 3. The benefits of metformin in PCOS

Metabolic/reproductive defects in PCOS	Benefits of metformin	Refs.
Blood pressure	Reduction	246
Insulin resistance	Reduction	252
Fasting insulin	Reduction	262
New onset of IGT	Reduction	250, 263
New onset of type 2 DM	Reduction	250
Fasting triglycerides	Reduction	262
Fasting cholesterol	+/−	262
Body weight, BMI, and waist circumference	Reduction	106, 247–249, 264
Serum androgens	Reduction	246, 252
Hirsutism scores	No effect	246, 308
Anovulation	Improvement	256, 309
Endothelial structure and function	Improvement	269, 310
IMT	Reduction	269, 310
Atypical endometrial hyperplasia	Improvement	24, 270, 311

levels in PCOS women (272). More recently, orlistat treatment in PCOS women, not only led to a significant improvement in insulin resistance indices and hormonal and metabolic profile, but also had a beneficial effect in reducing elevated advanced glycation end-products after 6 months of treatment, independently of BMI changes (273). Orlistat may therefore prove to be a useful adjunct in the treatment of PCOS. Another study showed that both metformin and orlistat had a similar effect on weight loss, ovulation rates, and androgen concentrations when applied in obese women with PCOS, supporting further the metabolic but also the reproductive benefits by orlistat usage in PCOS (274).

Sibutramine, a selective serotonin and adrenergic reuptake inhibitor, also has a positive effect on metabolic parameters in obese PCOS women (275). Waist-hip ratio and serum triglyceride levels were significantly reduced with sibutramine therapy, suggesting that sibutramine might have positive effects in obese women with PCOS (273). The effect of sibutramine on weight reduction and cardiometabolic factors has been extended in a recent study in obese women with PCOS. In this randomized, double-blind, placebo-controlled trial for 6 months, sibutramine together with lifestyle modification resulted in significant decreases in apolipoprotein B, apolipoprotein B/apolipoprotein A ratio and triglyceride levels (276). A recent study also demonstrated improvement in hyperandrogenemia after 6 months of treatment with sibutramine, providing another mechanism for the observed insulin resistance amelioration in sibutramine-treated PCOS women (277). Hence, in addition to the weight loss, sibutramine was assumed to have beneficial effects on reproductive profile. However, care must be exercised because it can cause a rise in blood pressure, which is not favorable in PCOS women who have a higher prevalence of systolic hypertension and cardiac dysfunction. Sibutramine was recently withdrawn from the market in both the United States and Europe as a result of increased cardiovascular risk associated with its use.

C. Bariatric surgery

A systematic review of 22,094 obese patients undergoing bariatric surgery (gastric banding, gastric bypass, gastroplasty, biliopancreatic diversion, or duodenal switch) has shown significant weight loss and improvement in metabolic perturbations, and a substantial majority of patients with diabetes, hyperlipidemia, hypertension, and OSA experienced complete resolution or improvement (278). The known cardiometabolic perturbations in women with PCOS led investigators to study the effect of bariatric surgery in women with PCOS. Morbidly obese women with PCOS undergoing biliopancreatic diversion or laparoscopic gastric bypass, demonstrated an average weight loss of 41 kg in 1 yr postoperatively, with significant improvement in hyperandrogenism and cardiometabolic perturbations (279). Similar findings were reported in women with PCOS undergoing Roux-en-Y gastric bypass procedure, where mean excess weight loss at 1 yr of follow-up was 56.7%, with significant improvement in hyperandrogenemia and metabolic disturbances (280). However, it should be noted that bariatric surgery, although much better in terms of outcomes, still has associated risks including nutritional abnormalities, infection, bowel obstruction, and mortality of just under 1%. But who should be offered bariatric surgery? In their recent consensus statement, the Androgen Excess and Polycystic Ovary Society recommend bariatric surgery 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 (224), based on the 1992 NIH Consensus Development Conference Statement (281). However, the criteria for bariatric surgery would, of course, depend on a number of other factors, including local and national guidelines.

XVI. Conclusions

The long-term health consequences of PCOS are a concern particularly in the background of the current obesity pandemic. In simple terms, these women are at greater risk for insulin resistance, type 2 diabetes, and vascular disease as compared with their non-PCOS counterparts. Thus, women with PCOS may require more regular screening for such risks as well as effective and targeted lifestyle advice

to prevent weight gain. The diagnosis and subsequent management of PCOS remains haphazard in the absence of a clear understanding of the pathophysiology of this disease. Although the majority of women with PCOS are overweight, it is likely that there is a significant proportion of women with this condition who behave different physiologically. Future research may tease out these subgroups and enable us to better manage these women based on their underlying pathophysiology. This review has addressed such issues and highlighted risk factors and aspects that are important for the management of PCOS. In so doing, it should act as a spur to clinicians, research scientists, and health care professionals to redouble their efforts into better understanding and so managing this enigmatic and increasingly prevalent condition.

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Address all correspondence and requests for reprints to: Dr. Harpal S. Randeva, MBChB, FRCP, Ph.D., Division of Metabolic and Vascular Health, Warwick Medical School, University of Warwick, Gibbet Hill Road, Coventry CV4 7AL, United Kingdom. E-mail: Harpal.Randeva@warwick.ac.uk.

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