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Review

Obesity, type 2 diabetes mellitus and cardiovascular disease risk: an uptodate in the management of polycystic ovary syndrome

Francesco Orio [a,b,*], Giovanna Muscogiuri [c], Cinar Nese [d], Stefano Palomba [e], Silvia Savastano [f], Domenico Tafuri [g], Giorgio Colarieti [h], Giovanbattista La Sala [e], Annamaria Colao [c], Bulent O. Yildiz [d]

[a] Department of Sports Science and Wellness, "Parthenope" University Naples, Naples, Italy
[b] Endocrinology and Diabetology, Fertility Techniques Structure, University Hospital "S. Giovanni di Dio e Ruggi d'Aragona", Largo Città d'Ippocrate, Salerno, Italy
[c] Ios and Coleman Medicina Futura Medical Center, Naples, Italy
[d] Department of Endocrinology and Metabolism, Hacettepe University School of Medicine, Ankara, Turkey
[e] Unit of Obstetrics and Gynaecology, Arcispedale Santa Maria Nuova, Istituto di Ricovero e Cura a Carattere Scientifico, University of Modena and Reggio Emilia, Reggio Emilia, Italy
[f] Department of Clinical Medicine and Surgery, University "Federico II" Naples, Italy
[g] Department of Exercise Science and Wellness, "Parthenope" University Naples, Naples, Italy
[h] Fertility Techniques Structure, "S. Giovanni di Dio e Ruggi d'Aragona" University Hospital Salerno, Salerno, Italy

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive aged women and is characterized by two of the following three features: oligoovulation or anovulation, clinical and/or biochemical signs of hyperandrogenism, or polycystic ovaries.
Summary: It has been demonstrated that PCOS includes a complex number of systemic symptoms in addition to symptoms related to the reproductive apparatus. It has been associated with obesity, metabolic syndrome, type 2 diabetes and an increased risk of cardiovascular disease. Several clinical and basic studies have investigated the link between PCOS and the cardiovascular disease risk, which seems to be due to blunted lipid/glucose metabolism, hypertension, and systemic inflammatory and coagulation disorders. Therefore, the current manuscript aims to review the main findings on PCOS and obesity/*obesity-related* disease (glucose derangements and cardiovascular disease risk factors).
Key message: Although there are no long-term data on the morbidity and mortality for cardiovascular disease in PCOS, it is advisable to perform a careful metabolic and cardiovascular assessment in women with PCOS in order to tailor the most suitable strategy to prevent cardiovascular disease.

Contents

* Corresponding author at: Via L. Vinciprova, 22, 84127 Salerno, Italy.
E-mail address: francescoorio@virgilio.it (F. Orio).

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive aged women with a prevalence of 6–10% based on the National Institute of Health (NIH) criteria and a prevalence as high as 15% when the broader Rotterdam criteria are used. PCOS is characterized by androgen excess, oligo-anovulation (O) and polycystic ovaries (P). According to the 1990 NIH criteria, the presence of both (1) oligo- and/or anovulation and (2) clinical (hirsutism) and/or biochemical signs of hyperandrogenism (H) are needed, regardless of the presence of P on ultrasound [1]. The 2004 Rotterdam criteria suggest that PCOS should be defined when at least two of the three features (O, H, and P) are present, with the exclusion of other etiologies that mimic PCOS [2].

PCOS is not only one of the main causes of infertility in women, but it is also considered as a plurimetabolic syndrome. In fact, PCOS is associated with long-term health risks, including insulin resistance/diabetes mellitus, obesity, alterations of the fibrinolytic system and dyslipidemia. These cardiovascular risk factors may often appear at an early age, suggesting that women with PCOS represent a large group at an increased risk for developing early onset cardiovascular disease (CVD) [3].

Therefore, PCOS is becoming a health care-related economic burden, in regards to the annual cost of evaluating and providing care to reproductive-aged women with PCOS in United States exceeds $4.3billion [4].

In this review we will focus on obesity in PCOS, with emphasis on *obesity-related* cardiovascular disease risk and glucose metabolism derangements.

Obesity and PCOS

Prevalence

Weight gain and central obesity are common features of PCOS and often precede the onset of anovulatory cycles. Visceral adiposity in PCOS is associated with greater insulin resistance (IR) resulting in exacerbation of the reproductive and metabolic abnormalities. Moreover, obesity has a major impact on PCOS phenotype since it is associated with a greater prevalence of menstrual irregularity, hyperandrogenemia and hirsutism [5].

The prevalence of overweight and obese women in PCOS is greater than that of the general female population. Conversely, the prevalence of PCOS increased in obese and overweight women compared to their lean counterparts. Alvarez-Blasco et al. [6] reported a 28.3% prevalence rate of PCOS in 113 overweight or obese women, who were referred to an endocrinology clinic for weight loss, compared with a previously reported 6.5% prevalence in the population [7], suggesting that the prevalence of PCOS might be markedly increased by obesity. In this study, the prevalence of PCOS was not related to the severity of obesity and was independent of the presence or absence of the metabolic syndrome thus suggesting that PCOS is not necessarily associated with obesity and metabolic syndrome [7]. On the other hand, Yildiz et al. [8] found that prevalence of PCOS was about 30% higher in unselected reproductive-aged women compared to the general population with moderate to severe obesity (12% vs. 9%), although this did not reach statistical significance. Moreover, the risk of PCOS was shown to be minimally increased with obesity [8]. The authors also reported that the degree of obesity of PCOS patients increased over time similar to the general population over a 15-year period, thus suggesting that obesity in PCOS is influenced by environmental factors [8]. However, in a recent study by Yildiz et al. [9], the prevalence rates of PCOS in obese women was found to be 2-fold higher or 3-fold higher compared to non-obese women according to the NIH or the Rotterdam criteria, respectively. In this study the prevalence of obesity was reported to be 15% according to Rotterdam criteria. This discrepancy may be due to different enrollment criteria of populations. The proportion of overweight PCOS women ranges from 10% in Italy to 37% in Kuwait, which supports widespread variability in the prevalence of overweight and obese women in PCOS populations among different countries. The highest prevalence of obesity associated to PCOS (61–76%) has been reported in the USA and Australia [10]. Ethnic origin also plays a significant role in the expression of features of PCOS, including prevalence and severity of obesity and metabolic disturbances. Asian women generally have been reported to have shorter stature and lower BMI compared to South Asians, African American and Hispanic women that displayed a higher prevalence of central obesity and metabolic syndrome [11].

Adipocytokines

Adipose tissue is the largest endocrine organ in the human body with many impacts on glucose homeostasis, steroid production, immune competence, hematopoesis and reproductive function. Adipose tissue produces a number of products including adipokines that are peptides acting as cytokines, chemokines, growth factors, and neurally active hormones. Some adipokines are secreted into the circulation (e.g., leptin) whereas others such as TNF-α function as paracrine or autocrine regulators. Several adipokines such as leptin, adiponectin, IL-6, plasminogen activator inhibitor (PAI) 1, visfatin, vaspin, resistin and TNF-α may play a role in the pathogenesis of obesity-related insulin resistance and also directly affect ovarian and adrenal function [12]. The exact role of these adipokines in the pathophysiology of PCOS is still unknown. The adipokines leptin and adiponectin, which play major role in glucose metabolism, will be addressed here in detail.

Leptin

Leptin is a 167-amino acid polypeptide that is synthesized predominantly by fat cells [14]. In a recent study by Lecke et al. [17], serum leptin level and subcutaneous leptin messenger RNA were found to be higher in overweight/obese PCOS women compared to normal-weight controls, and the authors reported that leptin/adiponectin ratio was significantly associated with percentage of body fat independent of BMI and free androgen index. Leptin was found in follicular fluid and leptin receptors are localized in preovulatory follicle, mature oocyte, granulosa, theca and interstitial cells. Elevated leptin levels are thought to be associated with the lack of follicular maturation. The concentration of leptin receptors was found to be similar in granulosa cells of PCOS women and of women undergoing in vitro fertilization for tubal disease, but the level of phosphorylated signal transducer and activator of transcription proteins was reported to be lower in PCOS suggesting that leptin signaling is disrupted in PCOS

[18]. Interestingly, in a recent study, it has been demonstrated that administration of the hormone leptin as an insulin sensitizing agent caused a reduction in testosterone levels and induced menses in lean women with PCOS and lipodystrophy [19].

In conclusion, PCOS, mostly when it is associated to overweight/obesity, is characterized by high levels of leptin, although the latter seems to be ineffective due to disrupted lepting signaling.

Adiponectin

Adiponectin is a 30 kDa protein that is the most abundant secreted adipokine from adipocytes. The potential role of adiponectin in the ovulatory dysfunction and metabolic abnormalities in PCOS has been investigated in several studies. Adiponectin at physiological levels induces expression of genes such as cyclooxygenase-2, prostaglandin E synthase and vascular endothelial growth factor, which are associated with periovulatory remodeling of the ovarian follicle. Plasma adiponectin levels are found to be correlated with insulin sensitivity in PCOS, independent of adiposity in some studies [20], whereas others failed to demonstrate this association [21]. In a study by Pangaribuan et al., it has been reported that serum adiponectin levels were reduced in obese women with PCOS, and that BMI, testosterone levels and IR were found to be major determinants of hypoadiponectinemia [22]. In the recent studies, it was shown that adiponectin affects the reproductive system through central effects on the hypothalamus-pituitary axis and through peripheral effects on the ovary and uterus, or directly on the oocyte and embryo. Adiponectin decreases LH secretion in pituitary gonadotropes and increases the secretion of progesterone and estradiol in human granulosa cells through an increase in p450 aromatase.

Genome-wide scan and linkage studies about the adiponectin gene reported a susceptibility locus for obesity, T2 DM and coronary artery disease. Particularly, two single nucleotide polymorphisms (SNPs), i.e. +45G15G(T/G) and +276(G/T), in exon 2 and intron 2 of the ADIPOQ gene (adipocyte C1q and collagen domain containing) respectively, were found to be strongly associated with T2DM, obesity and IR [23]. There is still controversy regarding the role of adiponectin gene polymorphism in women with PCOS. Zhang et al. [24] reported a higher prevalence of the +45G and +276G/T polymorphism in the adiponectin gene in women with PCOS compared to controls, while other studies failed to show this association [25]. Moreover, studies upon the effects of oral contraceptives or insulin sensitizers on adiponectin levels demonstrated that both adiponectin levels and insulin-stimulated glucose disposal increased when PCOS patients were treated with metformin or pioglitazone [26] while oral contraceptives caused a decrease in adiponectin levels [26].

In conclusion adiponectin could be considered as a marker of IR in PCOS. In fact adiponectin has been found to correlate with insulin sensitivity. Low adiponectin levels in PCOS contribute to increase cardiovascular risk.

PCOS in obesity

PCOS is a very common finding in obese women [27]. Azziz et al. estimated the prevalence of the different pathological conditions causing clinically evident androgen excess in a large consecutive population of patients. They found that 82% of the enrolled women were affected by PCOS and all the women affected by PCOS were obese [28]. Cupisti et al. performed a study in the same Azziz's experimental setting aiming to evaluate associations of clinical features, such as hirsutism, polycystic ovaries (PCOs), ovulatory dysfunction, and body mass index (BMI) R25 kg/m^2, with metabolic abnormalities in hyperandrogenic women. The results coming from this study showed that PCOS was a common finding in obese/overweight women [29]. Higher levels of BMI were associated to PCOS also in a study performed in three tundre forty women with hirsutism as the referral diagnosis [30]. German women with metabolic syndrome have been found to be affected by PCOS in 33% of cases [31].

Based on these data reporting the frequent association between obesity and PCOS, it could be suggested that screening for PCOS should be considered in obese women, mostly when they referred menstrual irregularities.

Type 2 diabetes mellitus and PCOS

Definition and diagnosis

IR is present in 50–80% of these women. IR is associated with obesity, but even lean PCOS women may have IR, that is secondary to a genetic disorder of insulin action. IR and pancreatic β-cell dysfunction are important risk factors for the development of T2DM in PCOS. This metabolic condition exists before puberty contributing to androgen excess state since compensatory hyperinsulinemia induces androgen secretion at the level of ovaries. On the other hand, it has been suggested that a state of excessive androgen secretion during fetal life might contribute to IR in PCOS patients by causing abdominal distribution of body fat and visceral adipose tissue dysfunction.

More than 2% of PCOS women have a risk of developing diabetes each year. To prevent metabolic and cardiovascular disease risk in women with PCOS, screening for these factors should start as early as possible and even at diagnosis. It has been suggested that BMI, WC and blood pressure should be measured at each visit. Women with PCOS have postprandial hyperglycemia most commonly reflecting peripheral IR. Therefore, 2-h post-challenge glucose values are suggested for the diagnosis of IGT and T2DM in PCOS. The AE-PCOS Society recommends that screening should be performed in obese patients or in lean patients with advanced age (>40 years) and patients with a history of gestational diabetes or with a family history of diabetes. The recommended initial screening test is either fasting plasma glucose or 75 g oral glucose tolerance test (OGTT) [32]. Recently, the American Diabetes Association (ADA) has included the level of glycated hemoglobin A1c (HbA1c) as a component of the diagnostic criteria for 'diabetes' (≥6.5% HbA1c) or 'increased risk for diabetes' (5.7–6.4% HbA1c). In agreement with ADA recommendations [33], the AE-PCOS society also included the HbA1c criteria for assessment of diabetes in PCOS. The measurement of HbA1C has several advantages compared to the FPG and OGTT that include greater convenience (fasting not required), greater preanalytical stability and less day-to-day variations during stress and illness. However, the use of HbA1C is limited by greater cost, the limited availability of HbA1C testing in certain regions of the developing world and the partial correlation between HbA1C and average glucose in certain individuals. The most appropriate time interval for re-screening of women with PCOS is also controversial. The ADA recommends diabetes screening for high risk patients including women with PCOS at least every 3 years, whereas some other organizations recommend re-screening every 1–2 years depending on the presence of co-existing risk factors.

Risk

The risk of development of IGT and T2DM in PCOS is investigated in many small-size studies. Legro et al. [34] failed to find a significant increase in the prevalence of IGT and T2DM from 37% to 45%, and from 10% to 15%, respectively, over a mean

follow-up period of 2–3 years in 71 women with PCOS and 23 controls. The authors did not find an association with weight gain. They also reported that nonobese PCOS women (BMI < 27 kg/m^2) were also at high risk of glucose intolerance (10.3 and 1.5% prevalence of IGT and T2DM, respectively). Another study including 67 overweight Australian women with PCOS, with a longer follow-up time (mean 6.2 years) reported an annual incidence of T2DM of approximately 2.5% [35]. In contrast, weight gain was found to be a predictor of glucose derangements in this study [35]. In a recently reported larger size study, including 21,170 women with PCOS and 89,636 controls matched for age, primary-care practice and BMI, it has been demonstrated that the incidence of T2DM was increased in PCOS compared to controls after a median follow-up period of 5 years [36]. BMI was found to have an important role in the development of diabetes, and with increasing BMI, a nonsignificant trend toward an increased crude rate of diabetes was also reported. Consistent with the findings of Legro et al. [34], the risk for the development of diabetes was significantly higher in the lean subgroup (hazard ratio: 1.4 for BMI < 25 kg/m^2). Weight gain was also reported to be associated with worsening glucose tolerance and a 1% increase in BMI lead to 2% increase in diabetes risk. The risk of diabetes was found to be higher in patients who were obese at baseline and remained obese for at least 2 years. The authors failed to show any association with the development of diabetes and the treatment with oral contraceptives or antiandrogens despite the reports that these may worsen insulin sensitivity [36]. Further, Möhlig et al. reported that the increased risk of diabetes associated to PCOS was not related to the endocrinological features of the syndrome but it was related to overweight/obesity that often accompanied this disease [37]. In contrast, metformin was found to be associated with an increased risk of diabetes, but this was linked to preferential prescribing to a population with more frequent insulin resistance, higher BMI and more frequent risk factors such as family history or previous gestational diabetes [36]. On the other hand, it is known that metformin reduces IR in women with PCOS and that it may reduce the conversion rate from normal glucose tolerance to IGT and T2DM in this population.

The prevalence of glucose derangements in PCOS may be also influenced by the different diagnostic criteria that were used. Patients diagnosed by the 1990 NIH classic criteria show higher rate of menstrual irregularity, hyperandrogenism, abdominal obesity and IR than those defined by non-NIH criteria. The prevalence of obesity and IR was found to be greater in classic PCOS patients than in those with ovulatory PCOS. Lifestyle modifications seem to play a key role in the management of glucose disturbances. A systematic review and meta-analysis including 9 trials enrolling 583 women suggested that lifestyle modifications decreased fasting blood glucose and insulin levels in women with PCOS and the obtained results were similar to the administration of metformin [38].

Different prevalence according to ethnicity

Women affected by PCOS have increased risk for developing T2DM and pre-diabetes (i.e., impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)) independent of BMI and age. The prevalence of hyperglycemia is increased with BMI, being highest in obese PCOS women (BMI > 30 kg/m^2). However, even lean women with PCOS have increased risk of IGT and T2DM [24]. 11–35% of PCOS patients are reported to have IGT and from 4% to 10% of the patients are reported to have T2DM [26,39,40]. The prevalence rate of IGT in PCOS was reported to be 3-fold higher than the population prevalence rate of IGT in women of similar age from the National Health and Nutrition Survey (NHANES) II, and twice the prevalence rate of IGT in age- and weight comparable reproductively normal control women [39]. Moreover, the prevalence rate of undiagnosed T2DM was found to be from 7.5 to 10-fold higher than the prevalence rate in NHANES II women of similar age [39]. The development of diabetes in PCOS may be significantly impacted by differences in population characteristics in studies from different countries. The prevalence of IGT and T2DM were as low as 6.4% and 0–2.3%, respectively, in two small Italian and Dutch studies [41,42].

In conclusion PCOS currently represents a risk factor for developing type 2 diabetes. Lean PCOS displayed the same degree of IR of overweight/obese healthy women, thus suggesting that IR is a common feature of PCOS. Based on these considerations, it is easy to understand the beneficial effects of metformin in the treatment of PCOS.

Cardiovascular disease risk and PCOS

Multiple risk factors for CVD including obesity, IR, dyslipidemia, arterial hypertension, coagulation disorders and hyperandrogenism may be found in young women with PCOS, although evidence for cardiovascular events in women with PCOS is limited.

Obesity, in particular, central obesity, contributes to worsen metabolic phenotype in PCOS. As it is well known, central obesity is involved in the secretion of several hormones and cytokines contributing to the onset of a proinflammatory state and oxidative damage that in turn, lead to endothelial dysfunction and to initiation and progression of atherosclerosis. Moreover, visceral fat plays a key role in the development of IR and lipid metabolism disorders. IR is very common in PCOS patients, occurring in approximately 60–80% of lean and 95% of obese women with PCOS [43]. IR is related to IGT and metabolic syndrome, two other predictors of T2DM and CVD [44]. A consequence of IR is an atherogenic lipoprotein profile, characterized by hypertriglyceridemia, increased low-density lipoprotein cholesterol (LDL-C) levels and decreased high-density lipoprotein cholesterol (HDL-C) levels. The impaired ability of insulin to suppress lipolysis increases mobilization of free fatty acids from adipose stores to liver, hampering insulin-mediated inhibition of hepatic very low-density lipoprotein cholesterol (VLDL-C) synthesis and blunting catabolism of VLDL-C [45]. Several studies examined the relationship of PCOS with dyslipidemia. In a study comparing women with PCOS to controls, higher LDL-C and lower HDL-C levels were found in PCOS women [46]. The association of PCOS and hypertension has been investigated, but controversial results have been reported. An increased prevalence of hypertension was described in obese PCOS patients [47], whereas it was not noticed in the lean PCOS [48], suggesting that obesity may be a confounding factor and the main determinant of hypertension in PCOS. Coagulation disorders constitute a risk factor for CVD. The association between coagulation disorders and PCOS provided conflicting results. Dahlgren et al. studied the coagulation profile in 28 PCOS women matched with 56 controls and they did not find any significant difference in term of PAI-1, vWF and factor VII activity [49]. Conversely, Yildiz et al. found an impairment of fibrinolysis in PCOS, reflected by the decrease of the global fibrinolytic capacity, that was not related to IR, therefore suggesting a protrombotic state in PCOS [50]. Lastly hyperandrogenism in itself may play a role in worsening IR and in the simultaneous development of central obesity in PCOS.

Low-grade chronic inflammation has also been implicated in the pathogenesis of cardiovascular disease risk in PCOS. Several markers of inflammation such as C reactive protein (CRP), fibrinogen and white blood cell count were found to be significantly increased in PCOS [51]. Moreover, CRP was found to be closely related to the degree of visceral fat accumulation. A direct correlation between CRP levels and aldosterone was found in

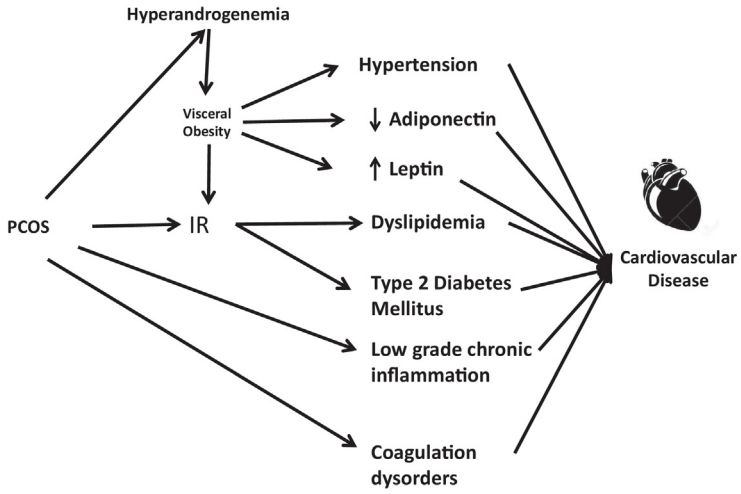

Fig. 1. Pathogenesis of cardiovascular disease in polycystic ovarian syndrome. Polycystic ovarian syndrome (PCOS) has been identified as a risk factor for cardiovascular disease. The multiple risk factors for cardiovascular disease that are associated with PCOS include type 2 diabetes, dyslipidemia, arterial hypertension, low grade chronic inflammation, increased leptin levels, decreased adiponectin levels and coagulation disorders.

PCOS, suggesting that aldosterone may induce inflammation followed by necrosis and subsequent reparative fibrosis inducing oxidative/nitrosative stress [52]. Acute phase reactants (CRP, fibrinogen and white blood cell count) were found to be independently associated with a direct measure of cardiorespiratory fitness (VO_{2max}) in 124 PCOS women suggesting that cardiopulmonary capacity may be strongly related to low grade inflammation in PCOS [53]. However, evidence of increased cardiovascular morbidity and mortality is inconsistent in PCOS. No increased prevalence of non-fatal/fatal cardiovascular events in PCOS was found in the report by Pierpoint et al. [54]. Conversely, the Women's Ischemia Evaluation Study reported that PCOS women had an increased prevalence of cardiovascular events, and in particular multivessel diseases, compared to non-PCOS women [55]. In support of this study, a greater coronary artery calcification prevalence was found in PCOS compared to controls in two studies [56]. Birdsall et al. found evidence of more advanced coronary artery diseases in PCOS women than women with normal ovaries, among 143 women undergoing coronary angiography for chest pain or valvular diseases. In addition to overt CVD, women with PCOS have evidence of more frequent subclinical vascular diseases vs. controls [57]. Early endothelial impairment was found by Orio et al. in 30 young normal-weight women with PCOS, who had no additional metabolic disorders or CVD. In particular, abnormal media thickness of carotid arteries, abnormal flow mediated dilation of brachial arteries and higher levels of plasma endothelin-1 were found in PCOS [58] (Fig. 1). These results have been recently emphasized by a meta-analysis that reported an impaired endothelial function as measured by flow-mediated dilation of the brachial artery, already at an early age [59]. A cross-sectional analysis using Truven Health Analytics MarketScan® Commercial databases from 2004 to 2011 assessed the association between women aged 18–64 years with and without PCOS and cardiovascular events. Women with PCOS were more likely to have aCVD, with stroke being the most prevalent manifestation [60].

In conclusion PCOS is associated to an increased cardiovascular risk. This is related to several factors. First, IR could be considered an important player in the pathogenesis of dyslipidemia associated to PCOS. Controversial results on the association of PCOS with hypertension have been reported while it seems to be a clear link between PCOS and early cardiovascular derangements such as endothelial dysfunction.

Conclusion

PCOS has been often associated to overweight/obesity and in turn PCOS is a common finding in overweight/obese subjects. Adipose tissue plays an important role in determining metabolic features of PCOS. In fact it has been demonstrated that the secretion of "*metabolic*" hormones such as leptin and adiponectin is modified in PCOS, respectively increasing and decreasing. This contributes to metabolic derangements associated to PCOS. The spectrum growing from insulin resistance to type 2 diabetes is commonly associated to PCOS, contributing to the increased cardiovascular risk identified as a risk factor for obesity, T2DM and CVD. Large-scale clinical trials evaluating the morbidity and mortality of CVD in PCOS subjects are lacking. Further, well-designed prospective controlled studies are still needed in order to predict the long term risk of developing T2DM and CVD. However, a careful metabolic and cardiovascular assessment is advisable in women with PCOS.

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