13 Cardiovascular Disease and Inflammation

Francesco Orio, Jr., MD, PhD,
Evanthia Diamanti-Kandarakis, MD, PhD,
and Stefano Palomba, MD

CONTENTS
INTRODUCTION
CARDIOVASCULAR DISEASE
INFLAMMATION
CONCLUSIONS
FUTURE AVENUES
KEY POINTS
REFERENCES

Summary
Polycystic ovary syndrome (PCOS) is not only a reproductive disorder, but also a complex, multifaceted, endocrine disease with several associated health complications. In fact, multiple lines suggest an increased cardiovascular risk and cardiovascular disease characterized by an impairment of cardiac structure and function, endothelial dysfunction, lipid abnormalities, and low-grade chronic inflammation. The increased prevalence of low-grade chronic inflammation in women with PCOS represents an emerging novel mechanism for cardiovascular disease in these women. All these features are likely linked to the insulin-resistance often present in women with PCOS. Cardiovascular disease and inflammation represent important long-term sequelae of PCOS that warrant further in-depth investigation.

Key Words: Cardiovascular disease (CVD); cardiovascular risk (CVR); inflammation; leukocytes; endothelial dysfunction; heart; inflammation.

INTRODUCTION
Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women, affecting 6–7% of women of reproductive age (1). PCOS is not only one of the main causes of infertility in women, but is also considered a plurimetabolic syndrome (2–4). Obesity (5), insulin-resistance (IR) (6), dyslipidemia (7), and an altered fibrinolytic system (8) are metabolic comorbidities often evident in the syndrome. Moreover, PCOS
is associated with long-term health risks, including type 2 diabetes mellitus (9) and cardiovascular disease (CVD) (10–14). In particular, IR, hyperandrogenism, and dyslipidemia are likely the major risk factors for the occurrence of CVD in PCOS. These cardiovascular risk (CVR) factors are often evident at an early age, suggesting that women with PCOS represent a large group of women at increased risk for developing early-onset CVD, even if this has not yet been confirmed in long-term studies (15).

The risk of coronary artery disease and myocardial infarction has been reported to be increased in patients with PCOS compared with regularly cycling women (10); however, to date, no prospective study of cardiovascular mortality in PCOS has been performed (16). Several studies (8,17–20) report alterations in intermediate end points for CVR in this population. In fact, endothelial (21) and diastolic (22) dysfunction have been demonstrated in PCOS and have been associated with both elevated androgen levels and IR. Recently, together with classical CVR factors, such as elevated total cholesterol (TC) levels and low high-density lipoprotein cholesterol (HDL-C) levels, obesity, elevated homocysteine, and left ventricular hypertrophy (LVH) have been shown to be independently associated with an increased CVR (23). The scientific interest vis-a-vis CVR in PCOS is increasing in recent years; in particular, biochemical, morphological, and functional markers of early CVD have been evaluated to correctly identify the CV morbidity of this syndrome. Several studies (17–20,24) have reported alterations in intermediate end points for CVR in women with PCOS, and have attempted to demonstrate an association between PCOS and CVR factors and CVD (Table 1). Furthermore, it is possible that genetic factors associated with PCOS could cause an increased CVR profile. One such factor is IR, which is considered the main factor leading to the development of the increased low-grade chronic inflammation and CVD in PCOS (Fig. 1).

**CARDIOVASCULAR DISEASE**

At the moment, there is no single, universally accepted definition for PCOS. This may be a contributing reason as to why published studies on PCOS have not yet provided a conclusive answer on the incidence of CVD in PCOS.

Women with PCOS represent an intriguing biological model of the effects of hormonal abnormalities on CVR. Several findings indicate a relationship between heart disease and PCOS, i.e., dyslipidemia (25), insulin resistance (6), increased left ventricular mass (LVM) (17), and diastolic dysfunction (14,22).

CVR factors and precocious cardiovascular abnormalities are often evident at an early age in PCOS, suggesting that the chronically abnormal hormonal and metabolic milieu found in women with PCOS, starting from adolescence, may predispose these women to premature atherosclerosis and making them candidates for early CVD.

Visceral obesity is present in about 50% of women with PCOS (1) and is a recognized risk factor for IR/hyperinsulinemia, dyslipidemia, type 2 diabetes, hypertension, coagulation abnormalities, and premature CVD. It can worsen all these metabolic and CV features present in PCOS, but it does not represent the only or the first etiopathogenetic factor for the increase of CVR in PCOS. As mentioned previously, IR is a determinant of overall CVR independent of obesity. In fact, increased CVR is related to the degree of IR among women with PCOS (26).