Understanding the link between Polycystic ovarian syndrome (PCOS) and dyslipidemia

Abstract

Polycystic ovarian syndrome (PCOS) is a heterogenous disorder characterized by signs and symptom of androgen excess and ovarian dysfunction in the absence of other diagnosis, with a prevalence of ~6%-~20%. This review is aimed at discussing the relationship that exists between PCOS and dyslipidemia. The aetiology of PCOS can either be unknown (primary) or originating from identifiable causes (secondary) like obesity, idiopathic hirsutism, epilepsy, androgen-secreting tumors etc. Weight gain especially around the stomach, missed, irregular or light menstruations, hyperandrogenism, infertility can serve as indicators for PCOS. With a prevalence report of about 70%, dyslipidemia, is related to PCOS, and its causes are multifactorial with many cases being undiagnosed due to different diagnostics criteria for PCOS. Studies revealed that women with PCOS showed increased levels of LDL-cholesterol, VLD Lipoprotein, ApoC-I, lipoprotein (a), decreased levels of HDL-cholesterol and ApoA-I while ApoB. Psychophysiology in dyslipidemia in PCOS include: obesity, hyperandrogenism. Insulin resistance. Diagnostic measures include: complete lipid profile test, pelvic ultrasound and transvaginal scan, hormone tests, glucose and insulin tolerance test, etc. There is no known cure of PCOS reported yet but there are different options on management which include lifestyle change, use of statin drugs if lifestyle modifications do not work, use of androgen inhibiting drugs and metformin might help. It is important and more advisable for the age range for PCOS testing to be reduced to accommodate females just entering puberty.

Keywords: *Dyslipidemia, Lipoprotein, PCOS*

INTRODUCTION

Polycystic ovary syndrome, or PCOS, is the most common endocrine disorder in women of reproductive age (Goodman *et al.,* 2015). It was first described by Antonio Vallisneri in 1721 (Speca *et al.,* 2007). The syndrome itself was later defined by Stein and Leventhal, based on their observation in 1935 (Stein& Leventhal, 1935). The syndrome is named after the characteristic cysts which may form on the ovaries, though it is important to note that this is a sign and not the underlying cause of the disorder (Dunaif& Fauser, 2013). PCOS is the most common cause of anovulatory infertility, meaning that the infertility results from the absence of ovulation, the process that releases a mature egg from the ovary every month. Many women don't find out that they have PCOS until they have trouble getting pregnant. PCOS can cause other problems as well, such as unwanted hair growth, dark patches of skin, acne, weight gain, and irregular bleeding. (Eunice Kennedy Shriver, (n.d.))

Dyslipidemia is an abnormal amount of lipids (e.g., triglycerides, cholesterol and/or fat phospholipids) in the blood (Dixon & Riche, 2020), it can also refer to unhealthy levels of one or more kinds of lipid (fat) in the blood. The blood contains three main types of lipids: high-density

lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides. If dyslipidemia is suspected, it usually means your LDL levels or your triglycerides are too high. It can also mean your HDL levels are too low. Dyslipidemia is a risk factor for the development of atherosclerotic cardiovascular disease (ASCVD) (Dixon & Riche, 2020).

Diagnostic Definition of PCOS

In 1990 a consensus workshop sponsored by the NIH/NICHD (National Institutes of Health/Eunice Kennedy Shriver National Institute of Child Health and Human Development) suggested that a person has PCOS if they have all of the following:(eMedicine (n.d)) oligoovulation, signs of androgen excess (clinical or biochemical), exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism.In 2003 a consensus workshop sponsored by ESHRE/ASRM (European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine) in Rotterdam indicated PCOS to be present if any two out of three criteria are met, in the absence of other entities that might cause these findings: (Teede*et al.,* 2010; Azziz, 2006;*Rotterdam ESHRE/ASRM* 2004) oligoovulation and/or anovulation, excess androgen activity, polycystic ovaries (by gynecologic ultrasound).

The Rotterdam definition is wider, including many more women, the most notable ones being women without androgen excess. Critics say that findings obtained from the study of women with androgen excess cannot necessarily be extrapolated to women without androgen excess. (Carmina, 2004; Hart *et al.,* 2004). In 2006, the Androgen Excess PCOS Society suggested a tightening of the diagnostic criteria to all of the following: (Teede*et al.,* 2010) excess androgen activity, oligoovulation/anovulation and/or polycystic ovaries, exclusion of other entities that would cause excess androgen activity.

Based on the aetiology PCOS can be classified as: ***Primary PCOS***which is the most prevalent type of PCOS without a recognized trigger. Based on the proposed idea, the hypothalamo-pituitary-ovarian axis is dysfunctional and functional ovarian hyperandrogenism (FOH) also exist. ***Secondary PCOS*** is the term used to denote PCOS that originates from readily identifiable causes other than HPO axis malfunction (Khadilkar, 2019).

There are four types of PCOS: Insulin-resistant PCOS, Inflammatory PCOS, and Pill-induced PCOS. Insulin-resistant PCOS is the most common type of PCOS. This type of PCOS can be due to smoking, sugar, pollution, and trans-fat. In this, high levels of insulin prevent ovulation and

trigger the ovaries to create testosterone. Pill- induced PCOS is the second most common PCOS. It gets developed due to the birth control pills which suppress ovulation. For most women, these effects do not last long and they resume ovulating after the effect of the pill is over. In PCOS due to inflammation, the following might occur: lack of ovulation, hormone imbalance and androgens production. Inflammation is caused due to stress, toxins of the environment, and inflammatory dietary like gluten. The symptoms such as headaches, infections, or skin allergies and your blood tests show that you are deficient in vitamin D, your blood count is not normal, increased levels of thyroid can indicate inflammatory PCOS. (Indira IVF Fertility and IVF Centre, 2022)

It is unclear what causes PCOS specifically. It is contended that high levels of male hormones inhibit the ovaries from producing eggs and hormones regularly and normally.A combination of genetic and environmental factors can predispose women to PCOS. (De Leo *et al.,* 2016; Dumesic*et al.,* 2015; Diamanti-Kandarakis*et al.,*2006)

Although the exact symptoms of this metabolic, endocrine, and reproductive illness are not known, the most prevalent ones are: menstrual disorders, ovaries that are large or have many cysts,hyperandrogenism with the most common signs being acne and hirsutism (male pattern of hair growth, such as on the chin or chest), weight gain especially around the belly (abdomen), infertility, small pieces of excess dark or thick skin on the neck, armpits and under the breasts (skin tags). (Teede*et al.,* 2010;Cortet-Rudelli&Dewailly, 2006)

Endometrial hyperplasia and endometrial cancer (eMedicine (n.d); Barry *et al.,* 2014), insulin resistance/type 2 diabetes (Moran *et al.,* 2010; Falcon & Hurd, 2007), high blood pressure particularly if obese or during pregnancy (Mayo clinic (n.d)), depression and anxiety (Teede*et al.,* 2010; Barry *et al.,* 2011), dyslipidemia (Ovalle & Azziz, 2002), cardiovascular disease (de Groot *et al.,* 2011), weight gain, miscarriage (Goldenberg & Glueck, 2008; Boomsma *et al.,* 2008), sleep apnea and non-alcoholic fatty liver disease particularly if obesity is present, *Acanthosis nigricans* (patches of darkened skin under the arms, in the groin area, on the back of the neck) (eMedicine (n.d)) can be associated with PCOS.

To produce steroid hormones, generate bile acids, or provide energy, lipids like cholesterol or triglycerides are absorbed from the intestines and transported throughout the body via lipoproteins. Triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein

cholesterol (LDL-C), and cholesterol are major contributions to these pathways. Dyslipidemia can originate from an imbalance of any of these elements, whether from organic or nonorganic causes. (Rader *et al.,* 1994)

Several health behaviors can have effects and increase lipid levels. This disorder can occur from food (the overwhelming intake of saturated fats or the minimal consumption of fruits, nuts, seeds, and vegetables.), tobacco use or exposure, genetics, physical inactivity, obesity, and it can cause serious problems like cardiovascular disease.Dyslipidemia can also result from diseases that run-in families. Most cases of familial hypercholesterolemia, which results in an increase in LDL-C levels, are caused by autosomal dominant mutations in LDL receptors. Although they are less frequent, other mutations in the cholesterol pathway have been found (Defesche*et al.,* 2017).Other common secondary causes of dyslipidemia include:Diabetes mellitus, chronic kidney disease, primary biliary cirrhosis and other cholestatic liver diseases, alcohol overuse, hypothyroidism,drugs such as thiazides, beta-blockers, retinoids, highly active antiretroviral agents, cyclosporine, tacrolimus, estrogen and progestins, and glucocorticoids. Secondary causes of low levels of HDL cholesterol include cigarette smoking, anabolic steroids, HIV infection, and nephrotic syndrome.

Dyslipidemia itself usually causes no symptoms but can lead to symptomatic vascular disease, including coronary artery disease (CAD), stroke, and peripheral arterial disease.Acute pancreatitis can be brought on by having high levels of triglycerides (> 500 mg/dL [> 5.65 mmol/L]). Additionally, hepatosplenomegaly, paresthesias, dyspnea, and disorientation can all result from extremely high triglyceride levels.Elevated degrees of LDL can cause arcus corneae and tendinous xanthomas at the Achilles, elbow, and knee ligaments and over metacarpophalangeal joints.Other clinical discoveries that happen in patients with high LDL (eg, in familial hypercholesterolemia) incorporate xanthelasma (lipid rich yellow plaques on the average eyelids). Xanthelasma can likewise happen in patients with essential biliary cirrhosis and ordinary lipid levels.

Fig 2. Xanthomas (Ladizinski*et al.,* 2013)

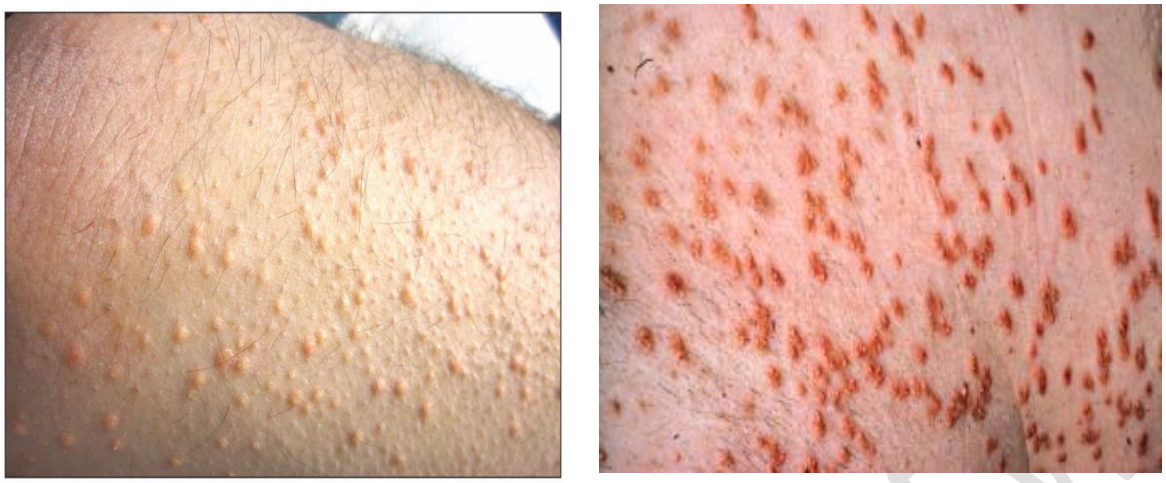

Fig 1.Dyslipidemia

PREVALENCE OF DYSLIPIDEMIA IN PCOS

Dyslipidemia is a prevalent metabolic disorder associated with PCOS, albeit the types and degrees of lipid abnormalities that have been documented have varied (Rajkhowa *et al*., 1997;Talbott *et al.*, 1995; Wild *et al.,* 1985). About 70% of PCOS patients have abnormal serum lipid levels, per recommendations from the third report of the National Cholesterol Education Program (NCEP) (2002). Ethnicity can be a significant factor among the several genetic and behavioral factors implicated in the existence of dyslipidemia (Carmina *et al.,* 2003). In a recent study, 36% of patients with the classic PCOS phenotype (hyperandrogenism and chronic anovulation) from the Mediterranean region presented with an altered lipid pattern, a much lower percentage than that found in US subjects (Carmina *et al.,* 2003).Another significant component linked to the dyslipidemia of PCOS is IR (insulin resistance). 46% of women with PCOS had the metabolic syndrome. Lipid abnormalities were discovered to be very prevalent in this subset of women. High-density lipoprotein (HDL) values were lowered in 95% of these women, although hypertriglyceridemia was present in 56% of them. (Glueck *et al.*,2003)

RELATIONSHIP BETWEEN PCOS AND DYSLIPIDEMIA

Dyslipidemia is common in PCOS compared to weight matched controls (Meyer *et al.,* 2005; Talbott *et al.,* 1998; Wild RA. 1995; Wild *et al.,* 1985), with higher triglycerides and lower high-density lipoprotein cholesterol (Wild *et al.,* 1985).With a prevalence of up to 70%, dyslipidemia is a fairly prevalent metabolic disorder in women with PCOS (Legro *et al.,* 2001). Dyslipidemia

may be the most common cause of PCOS in women before the age of 40 years. Although dyslipidemia occurs independent of body mass index (BMI) (Wild *et al.*,1988; Wild *et al.*, 1985), however there is a synergistic deleterious effect of obesity and insulin resistance in PCOS analogous to that seen in DM2. The causes of dyslipidemia in PCOS are again multifactorial. Insulin resistance appears to have a pivotal role mediated in part by stimulation of lipolysis and altered expression of lipoprotein lipase and hepatic lipase (Wild *et al.*, 1985).

In recent meta-analysis,there were noticeable decrease in HDL-C and increase in TG levels in women with PCOS (Kim 2013; Dejager 2001; Legro *et al.*, 2001). Triglycerides and low-density lipoprotein (LDL) cholesterol levels were 26 mg/dL and 12 mg/dL higher, and high-density lipoprotein cholesterol concentration was 6 mg/dL lower in women with PCOS than those of controls. Changes in LDL quality also have been reported in women with PCOS: women with PCOS have an increased proportion of atherogenic small dense LDL or decreased mean LDL particle size.Lipoprotein has been distinguished as a free gamble factor for coronary illness, and its height in PCOS patients has been reliably detailed in different examinations including non-stout Korean populace. A few examinations have explored apolipoprotein (Apo) A-I and ApoC-I levels in ladies with PCOS and levels of ApoA-I, which has cardio-defensive impacts, were essentially lower in ladies with PCOS than those of controls. ApoC-I is known to expand the postprandial serum lipid level that is normal in coronary artery disease patients, and one review detailed that such a height might be the earliest variety of lipid anomaly in ladies with PCOS (Kim *et al.*, 2013). Decrease in HDL-C and increase in TG levels are well known lipid profile characteristics in women with PCOS (Kim 2013; Dejager 2001; Legro *et al.*, 2001).In an analysis, TG levels were higher and HDL-C concentrations were lower in women with PCOS than those of with PCOS. This was also supported by Wild *et al.* (2011) who had similar finding.

The ability of different HDL subclasses to provide cardio-protection is known to vary. HDL2 has been identified as the most antiatherogenic HDL subtype by studies conducted by many researchers, and decreased levels of this lipoprotein have therefore been strongly associated with coronary heart disease, even in non-obese individuals (Warnick *et al.*, 2001).Talbott *et al.* (1995) enlisted a sum of 206 ladies with PCOS and 206 age-matched controls, and complete HDL and HDL2 levels were essentially lower in ladies with PCOS than controls even subsequent to controlling for both age and BMI. Conway *et al.* (1992) additionally found that even lean ladies

with PCOS had decreased serum HDL and HDL2 focuses contrasted with controls. These discoveries recommend that ladies with PCOS have low serum HLD-C levels, yet additionally show adjustments in HDL quality.

Although the cause of the elevated LDL-C levels in women with PCOS is yet unknown, they may be linked to hyperandrogenism or a genetic component.LDL-C is increased in women with PCOS; however, recently, alterations in LDL quality also have been reported in women with PCOS (Dejager *et al.,* 2001) (Sidhwani*et al.,* 2011;Doi *et al.,* 2008; Berneis*et al.,* 2007; Pirwany*et al.,* 2001). LDL comprises different subclasses according to size, density and atherogenicity. Small dense LDL particles are more atherogenic than large buoyant ones, and are strongly associated with coronary artery disease (National Cholesterol Education Program (NCEP) 2002). Women with PCOS have an increased proportion of atherogenic small dense LDL or decreased mean LDL particle size (Dejager *et al.,* 2001) (Sidhwani*et al.,* 2011; Doi *et al.,* 2008; Berneis*et al.,* 2007; Pirwany*et al.,* 2001) and such alterations may be associated with increased cardiovascular risk as seen on a study done only on obese women or over-weight women, but on a study done on non-obese Korean women, the findings suggest that non-obese Korean women with PCOS have no significant quantitative or qualitative changes in LDL-C profile (Kim *et al.,* 2013).

Berneis*et al.,* (2009) also reported that lipoprotein (a) abnormalities may be found in one-third of Mediterranean women with PCOS who have a normal lipid pattern, which was similar with previous results. The prevalence of dyslipidemia in different PCOS phenotypes were investigated and also reported that levels of lipoprotein (a) were significantly increased in anovulatory women with PCOS than ovulatory women (Rizzo *et al.,* 2009). Thus, they concluded that measurement of lipoprotein (a) in women with different PCOS phenotypes may potentially help to assess cardiovascular risk.

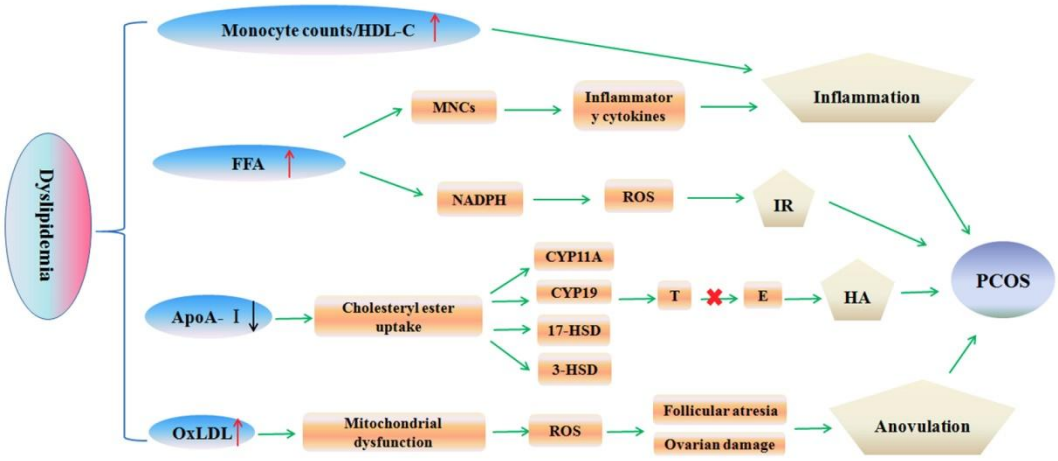

Figure 3. The influences of lipid abnormalities in PCOS. Green arrow represents potential interaction; red cross represents no conversion; Apo-AI: apo-lipoprotein AI; E: estradiol; FFA: free fatty acid; HDL-C: high-density lipoprotein cholesterol; HA: hyperandrogenism; IR: insulin resistance; MNCs: mononuclear cells; NADPH: nicotinamide adenine dinucleotide phosphate; OxLDL: oxidized LDL; PCOS: polycystic ovary syndrome. ROS: reactive oxygen species; T: testosterone.

PATHOPHYSIOLOGY OF DYSLIPIDEMIA IN PCOS

Among a cluster of interrelated risk factors present in PCOS, the determination of the causes and their intercalated effects on dyslipidemia has proven to be an exceedingly difficult task.

Obesity: Among the suggested mechanisms underlying dyslipidemia in obesity are overproduction of VLDL particles and defective lipoprotein lipase (LPL)-mediated lipolysis.Women with PCOS tend to have an increased waist-to-hip ratio (i.e., centripetal fat distribution), rendering them more susceptible to dyslipidemia, because centrally located adipocytes appear to exert an adverse effect on blood lipids (Yildirim *et al.,* 2003). Strikingly, intra-abdominal visceral fat accumulation might contribute to lipid metabolism disorders even in non-obese PCOS patients (Yildirim *et al.*, 2003).

Hyperandrogenemia: Hyperandrogenism and lipid metabolism are intimately related; however, the pathogenetic mechanisms involved have not yet been defined. One study reveals striking effects of testosterone on adipocytes isolated from subcutaneous adipose tissue of PCOS women (Cordbould*et al.*, 2007). In particular, testosterone was shown to induce androgen receptor (AR)-

mediated IR. Androgens affect lipoprotein metabolism in several steps. Testosterone has been implicated in lowering HDL levels (Whitsel *et al.*,2001). HDL metabolism is a complex process involving HDL-remodeling enzymes, lipid transfer proteins and cell surface receptors, which could constitute a potential target for androgens.

Insulin resistance: Clinical observations confirm the association of Insulin resistance and dyslipidemia in PCOS. PCOS women with Diabetes Mellitus type 2 (DM2) had a significantly greater prevalence of lipid abnormalities (88%) than did women with PCOS with normal glucose tolerance (58%). Additionally, 81% of insulin resistant PCOS patients demonstrated lipid abnormalities, compared with 65% of those with normal insulin sensitivity (Legro *et al.*, 2001).

DIAGNOSIS

The Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society has recommended that women with PCOS receive a complete lipid test (total cholesterol, LDL-C, non-HDL-C, HDL-C, and TG) (Kim *et al.*, 2013). Current studies have shown that age, WC (waist circumference), insulin, FSH (follicle-stimulating hormone), and SHBG (sex hormone-binding globulin) were predictors for dyslipidemia in women with PCOS (Luo *et al.*, 2021), therefore it is not far-fetched to test for these parameters for diagnosis. Not every person with PCOS has polycystic ovaries (PCO), nor does everyone with ovarian cysts have PCOS; although a pelvic ultrasound is a major diagnostic tool, it is not the only one (eMedicine (n.d)). The diagnosis is fairly straightforward using the Rotterdam criteria, even when the syndrome is associated with a wide range of symptoms (Lujan *et al.*, 2008). History-taking, specifically for menstrual pattern, obesity, hirsutism and acne. A clinical prediction rule found that these four questions can diagnose PCOS with a sensitivity of 77.1% and a specificity of 93.8% (Perdersen *et al.*, 2007). Serum (blood) levels of androgens, including androstenedione and testosterone may be elevated (Teede*et al.*, 2010). The free testosterone level is thought to be the best measure, (eMedicine (n.d);Sharquie*et al.*, 2007) with approximately 60 per cent of PCOS patients demonstrating supranormal levels (Huang *et al.*, 2010). The ratio of LH (luteinizing hormone) to FSH (follicle-stimulating hormone), when measured in international units, is elevated in women with PCOS. There are often low levels of sex hormone-binding globulin, (eMedicine (n.d)) in particular among obese or overweight women (Macpherson 2002). Anti-Müllerian hormone (AMH) is increased in PCOS, and may become part of its diagnostic criteria. (Dumont *et al.*, 2015; Dewailly*et al.*, 2014; Broer *et al.*, 2014). Two-hour oral glucose tolerance test (GTT) in women

with risk factors like obesity, family history, history of gestational diabetes (Teede*et al.*, 2010) may indicate impaired glucose tolerance (insulin resistance) in 15–33% of women with PCOS. (eMedicine (n.d)). Elevated insulin levels have been helpful to predict response to medication and may indicate women needing higher doses of metformin or the use of a second medication to significantly lower insulin levels. Elevated blood sugar and insulin values do not necessarily predict who responds to an insulin-lowering medication, low-glycemic diet, and exercise. Many women with normal levels may benefit from combination therapy. A hypoglycemic response in which the two-hour insulin level is higher and the blood sugar lower than fasting is consistent with insulin resistance. A mathematical derivation known as the HOMAI, calculated from the fasting values in glucose and insulin concentrations, allows a direct and moderately accurate measure of insulin sensitivity (glucose-level x insulin-level/22.5). (Muniyappa*et al.*, 2000)

PCOS has no cure, as of 2020 (Eunice Kennedy Shriver National Institute of Child Health and Human Development (n.d)).Treatment may involve lifestyle changes such as weight loss, exercise (Mortada & William, 2015; Giallauria*et al.*, 2009) and diet. National Institutes of Health (NIH) in 2014 reported that birth control pills may help with improving the regularity of periods, excess hair growth, and acne, Metformin and anti-androgens may also help. Statin drugs are used when lifestyle modifications are not enough, and have emerged as a novel therapeutic approach to PCOS. In addition to improvement of lipid profiles, PCOS women receiving statins has shown a significant decrease of testosterone, free androgen index, C-reactive protein, and insulin resistance (Wild *et al.*, 2010; Banaszewska *et al.*, 2007;Sathyapalan*et al.*, 2009). However, the use of statins in pregnancy is contraindicated, and contraception is required.

CONCLUSION

PCOS, a complex heterogeneous entity, is associated with an atherogenic lipoprotein profile, characterized by elevated triglyceride-rich lipoproteins, increased small dense LDL and depressed HDL. Insulin resistance is classically related to these changes and hyperandrogenemia might contribute to low HDL levels by stimulating hepatic lipase activity. Dyslipidemia is one of the most perplexing metabolic consequences, and, in conjunction with IR, increases the risk for diabetes and cardiovascular disease in women with the syndrome (Diamanti-Kandarakis*et al.*, 2007). Women with PCOS have both quantitative and qualitative changes in LDL-C profile: not

only increased LDL-C level but also increased proportion of atherogenic small dense LDL, ApoA-I, ApoC-I, and lipoprotein (a) abnormalities were also reported. (Kim & Choi,2013)

Dyslipidemia in PCOS occurs within a cluster of several interrelated pathological modalities, including obesity, hyperinsulinemia and hyperandrogenemia. Despite the difficulties in defining the cause-and-effect relationship between these factors, it seems that each one has independent, as well as inter-related, effects on the abnormal lipid profile in PCOS. (Diamanti-Kandarakis*et al.*, 2007)

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