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Statins: Do they have potential in the treatment of polycystic ovary syndrome?

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Abstract

Many women of reproductive age are affected by polycystic ovary syndrome (PCOS), a heterogeneous endocrinopathy characterized by androgen excess, chronic oligo-anovulation and/or polycystic ovarian morphology. In addition, PCOS is often associated with insulin resistance, systemic inflammation and oxidative stress which, on one hand, lead to endothelial dysfunction and dyslipidemia with subsequent cardiovascular sequelae and, on the other hand, to hyperplasia of the ovarian theca compartment with resultant hyperandrogenism and anovulation. While traditionally statins have been used to treat dyslipidemia by blocking HMG-CoA reductase, the rate limiting step in cholesterol biosynthesis; in fact, they possess pleiotropic actions, resulting in antioxidant, anti-inflammatory and anti-proliferative effects. Statins offer a novel therapeutic approach to PCOS in that they address the dyslipidemia associated with the syndrome, as well as hyperandrogenism/hyperandrogenemia. These actions may be due to an inhibition of the effects of systemic inflammation and insulin resistance/hyperinsulinemia. Evidence to date, both in vitro and in vivo, suggests that statins have potential in the treatment of PCOS; however, further clinical trials are needed before they can be considered a standard of care in the medical management of this common endocrinopathy.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age with prevalence rates estimated at between 6-10% [1]. As PCOS represents a heterogeneous endocrinopathy, its diagnosis is often hampered by controversy regarding its definition. Recent consensus favors the National Institutes of Health (NIH) criteria for PCOS, which includes women with a combination of 1) hyperandrogenism or hyperandrogenemia and 2) oligo- or anovulation in the absence of other etiologies for these symptoms, such as Cushing's syndrome, thyroid disorders, or congenital adrenal hyperplasia, among others [2]. PCOS is, in effect, a diagnosis of exclusion.

While the above definition describes a more severe form of PCOS, the Rotterdam consensus definition coined during the 2003 Annual Meeting of the European Society of Human Reproduction and Embryology (ESHRE) adds to the NIH criteria two additional subsets of

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women, who have a partial PCOS syndrome based on the presence of polycystic ovarian appearance on ultrasound [3]. According to the Rotterdam definition, any two of the three criteria (hyperandrogenism, anovulation, and/or polycystic ovarian appearance) are sufficient to make a diagnosis of PCOS. Therefore, this definition broadens the NIH criteria by including 1) women with polycystic ovaries and hyperandrogenism, but no ovulatory dysfunction and 2) women with oligo-anovulation and polycystic ovaries, but no evidence of androgen excess. The inclusion of these two phenotypes as a part of PCOS is debatable, as there is less convincing evidence to show that they lead to the metabolic complications associated with PCOS defined by the NIH criteria [2].

In 2006, the Androgen Excess Society weighed in on the controversy over the diagnostic criteria for PCOS and recommended the presence of clinical and/or biochemical hyperandrogenism and either 1) oligo-anovulation or 2) polycystic ovarian morphology to make the diagnosis [2]. As illustrated by the Venn diagram in Figure 1, PCOS may be viewed as a spectrum of disorders including the complete syndrome, but also various partial syndromes. It is unclear whether the so-called partial syndromes are part of a continuum that can lead to full-blown PCOS or whether they are milder, genetically/etiologically distinct forms of PCOS with potentially less significant sequelae. The genetic basis for PCOS is an area of active investigation with more than 70 candidate genes identified thus far and significant familial clustering [4, 5].

Whether the syndrome is partial or complete, women with PCOS suffer from many consequences, including those related to hyperandrogenism, ovulatory dysfunction, polycystic ovarian appearance, and cardiovascular risks. While not part of the diagnostic criteria, obesity and insulin resistance are also very common among women with PCOS and have long-term sequelae. This review will address the various clinical manifestations of PCOS as well as its pathophysiology. Subsequently, the rationale and evidence for the use of statins for the potential treatment of this syndrome will be introduced and discussed in detail.

Consequences of hyperandrogenism

Hyperandrogenemia or clinical manifestations of hyperandrogenism, such as hirsutism, male-pattern balding, and acne, are common among women with PCOS. In fact, up to 90% of women with PCOS have elevated androgen levels [6]. With respect to hirsutism, androgens are involved in the irreversible transformation of fine vellus hairs into coarse terminal hairs [7]. Androgens also contribute to the pathogenesis of acne vulgaris in that androgen receptors and 5-alpha reductase, the enzyme that transforms testosterone to the more potent dihydrotestosterone (DHT), are both present within the sebaceous follicle [8, 9]. Left untreated, hyperandrogenism can lead to long-term psychological sequelae, for example, related to facial scarring from acne [10].

Androgen excess may also contribute to the cardiovascular risks associated with PCOS, which will be discussed below. For instance, the dyslipidemia of PCOS correlates with hyperandrogenemia [11], and treatment of the latter leads to improvements in lipid profile [12, 13]. Hyperandrogenemia also represents an independent risk factor for the development of hypertension among women with PCOS [14]. Furthermore, androgen excess may lead to decreased insulin sensitivity as seen in women with congenital adrenal hyperplasia [15]and among those treated with exogenous testosterone [16]. A recent study of postmenopausal women with current hyperandrogenemia and a history of oligomenorrhea showed an increased rate of Type II diabetes, metabolic syndrome, and angiographic evidence of coronary artery disease with decreased 5 year cardiovascular event-free survival compared to women without clinical features of PCOS [17].

PCOS is a frequent cause of female infertility [18]. According to a 31- year follow-up study, almost 18% of women with PCOS were infertile compared to 1.3% among their age-matched counterparts [19]. Poor reproductive function among women with PCOS is due to anovulation as well as a high rate of early pregnancy loss [20, 21]. In addition to infertility, a consequence of the chronic anovulation associated with PCOS is endometrial hyperplasia, which can progress to endometrial adenocarcinoma. Endometrial hyperplasia has been reported to occur in up to 35% of untreated women with PCOS. While increased mortality risk from endometrial carcinoma among women with PCOS remains controversial [19, 22, 23], an association between the presence of polycystic ovaries and endometrial carcinoma was recently documented among patients less than 50 years old undergoing surgery for the latter [24].

Consequences of polycystic ovarian appearance

The current sonographic definition of polycystic ovaries requires the presence of 12 or more follicles measuring 2-9 mm in diameter per ovary or ovarian volume above 10 cc^3. This finding is seen in 20% of women who do not meet other criteria of PCOS. Conversely, and as alluded to above, not all women with PCOS have polycystic ovarian morphology. Nevertheless, the polycystic appearance of ovaries has important prognostic value not only in regard to the risk of endometrial carcinoma as mentioned above [24], but also with respect to treatment of anovulation. Women with polycystic ovaries have an increased chance of having a multiple gestation after ovulation induction and also are at higher risk for the development of ovulation hyperstimulation syndrome (OHSS). One recent study reported a 36% multiple gestation rate among PCOS patients, who underwent ovulation induction with gonadotropins [25]. The risk of moderate to severe OHSS among women with PCOS undergoing in vitro fertilization has been estimated to be 10.5% compared to less than 4% among non-PCOS patients [26]. This increased risk can be predicted by the polycystic ovarian appearance on baseline ultrasound; a recent meta-analysis found an almost 7-fold increased risk for the development of OHSS among women with polycystic ovaries compared to controls with sonographically normal appearing ovaries [27].

Consequences of obesity and insulin resistance

Among women diagnosed with PCOS in the United States, 60% are obese [28]. Insulin resistance with resulting hyperinsulinemia also occurs frequently among both lean and obese women with PCOS, and glucose intolerance rates of up to 40% have been reported [29-31]. Furthermore, type 2 diabetes is diagnosed in approximately 10% of women with PCOS [29-31], and while impaired glucose tolerance and type 2 diabetes are most common among women with PCOS who are in their thirties or forties, a significant percentage of adolescents with PCOS are also affected [32]. The implications of obesity and insulin resistance in the setting of women with PCOS are many.

During pregnancy, obesity is associated with various maternal-fetal complications, including gestational hypertension, preeclampsia, gestational diabetes, fetal macrosomia, shoulder dystocia, and failure to progress in labor requiring Cesarean section [33-36]. Among obese women, the latter is complicated by an increased risk of intra-operative hemorrhage, postpartum endometritis, and wound infection[37]. In addition, most anesthesia-related complications leading to maternal morbidity and mortality occur in the obese gravida [38-40]; in one study, 75% of anesthesia related maternal deaths occurred in obese women [41]. Similarly, preexisting insulin resistance confers an increased risk for gestational diabetes with its associated maternal and fetal consequences, including polyhydramnios, fetal macrosomia, birth trauma, operative delivery, and neonatal metabolic complications and higher perinatal mortality [42, 43].

Outside of pregnancy, the consequences of obesity and insulin resistance are their associations with cardiovascular disease. Specifically, both obesity and insulin resistance predispose women with PCOS to endothelial dysfunction [44-46], and obese, insulin-resistant women with PCOS have metabolic profiles consistent with dyslipidemia [47, 48]. Obesity and insulin resistance also represent independent risk factors for the metabolic syndrome, which will be discussed below.

Cardiovascular risks

In the long-term, women with PCOS are at increased risk for dyslipidemia, hypertension, and related cardiovascular morbidity and possibly mortality [49-51]. The dyslipidemia of PCOS is characterized by elevated plasma levels of cholesterol, low density lipoproteins (LDL), very low density lipoproteins (VLDL), and triglycerides with concomitantly reduced concentrations of high density lipoproteins (HDL) [52-55]. Homocysteine levels are also higher in women with PCOS compared to controls[56-59], and hyperhomocysteinemia represents another independent risk factor for the development of cardiovascular disease[60]. Moderate hyperhomocysteinemia predisposes individuals to endothelial dysfunction via a mechanism involving increased oxidative stress [61].

Both symptomatic and asymptomatic women with PCOS have signs of significant vascular impairment. For example, common carotid artery vascular compliance is decreased, while arterial stiffness is increased [62], and endothelial dysfunction manifests as impaired vasodilation in hyperandrogenic, insulin-resistant women with PCOS when compared with age- and weight-matched controls [63]. PCOS is also associated with increased thickness of arterial intima-media and greater prevalence of subclinical significant occlusion in more arterial segments compared to women with normal appearing ovaries [54]. A recent study non-invasively assessed coronary artery calcium (CAC) by computed tomography and reported that 33% of young obese women with PCOS had evidence of early coronary atherosclerosis compared to 8% of age and weight matched controls [64]. The presence and quantity of CAC is directly related to the risk of subsequent coronary events, namely, myocardial infarction and sudden death, in both asymptomatic and symptomatic patients [65]. One study found that women with PCOS had a 7-fold increased risk for myocardial infarction [52].

The Metabolic Syndrome

A major risk factor for the development of cardiovascular disease is the metabolic syndrome, which consists of a combination of factors, including obesity, dyslipidemia, hypertension, and glucose intolerance [66]. According to the National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP III), metabolic syndrome in women is defined as the presence of at least three of the following: waist circumference > 88cm, serum triglycerides > 150 mg/dl, serum HDL < 50 mg/dl, blood pressure greater than 130/85, and serum fasting glucose over 110/mg/dl [67].

Among the 7 to 10 million American women with PCOS, the prevalence of the metabolic syndrome is approximately 43%, which is 2-fold higher than that for age-matched controls [68]. A recent study found an 11-fold increase in metabolic syndrome in women with PCOS, and even young women (<30 years old) had a significantly higher risk [69]. The most prominent metabolic syndrome features among women with PCOS are, in decreasing order, decreased HDL levels, obesity, and hypertension [68].

Insulin resistance, one of the major causative factors involved in the development of metabolic syndrome [70], is prevalent in both lean and obese women with PCOS and potentiates the dyslipidemia, obesity, and glucose intolerance associated with this disorder. Due to the high prevalence of impaired glucose tolerance among women with PCOS, the Androgen Excess

Society recently issued a position statement urging providers to screen all PCOS patients for impaired glucose tolerance using a 2-hour oral glucose tolerance test at least once every two years [71].

Despite the multitude of cardiovascular risk factors associated with PCOS, increased mortality due to cardiovascular disease has not been clearly demonstrated among this population [19, 72]. However, given that long-term data are lacking and PCOS affects many women of reproductive age, the increased risk for cardiovascular disease in the long-term is concerning.

Pathophysiology of PCOS

While the root causes of PCOS are still not known, a broad range of interactions between endocrine and metabolic derangements have been described. Thus, for example, the etiology of anovulation in PCOS is multifactorial and includes alterations in ovarian, hypothalamic and pituitary function. Most women with PCOS have elevated plasma concentrations of luteinizing hormone (LH) and normal or decreased serum levels of follicle-stimulating hormone (FSH) [73]. The LH-enriched milieu promotes thecal steroidogenesis and thus contributes to the hyperandrogenism typically seen with this disorder. In addition, there is a strong association between insulin resistance and hyperandrogenism, and most evidence indicates that hyperinsulinemia induces hyperandrogenism [74, 75].

Insulin stimulates the production of androgens by ovarian thecal and stromal cells [76]. PCOS is also associated with increased levels of bio-available insulin-like growth factor I (IGF-I) [77-80], and both insulin and IGF-I not only induce proliferation of theca-interstitial cells [81-84], but also prevent these cells from undergoing apoptosis [85]. Thus, excessive androgen production in PCOS may be due, in part, to stimulation of the proliferation of the theca-interstitial compartment by insulin and IGF-I. In addition to stimulating ovarian steroidogenesis, elevated insulin levels inhibit hepatic production of SHBG and thereby further increase bioavailable androgens [86]. Excess insulin has other untoward metabolic effects, including those on muscle, fat, and the vasculature as discussed above.

The molecular basis for insulin resistance, though not yet fully understood, may be related to a post-receptor defect involving oxidative stress-mediated serine phosphorylation of the insulin receptor substrates 1 and 2 (IRS-1, IRS-2), which leads to an abrogation of insulin signaling via its receptor [87, 88]. Specifically, serine phosphorylated IRS molecules lose efficacy in binding to the insulin receptor as well as downstream targets, and this leads to impaired insulin action with compensatory hyperinsulinemia [89, 90]. In addition, when phosphorylated, IRS molecules are more susceptible to degradation [89, 90]. The alterations in IRS function and integrity result in impaired metabolic effects of insulin, particularly with respect to glucose transport, but paradoxically, the mitogenic effects of insulin persist [91]. In fact, certain mitogenic pathways, including those involving the mitogen activated protein kinase (MAPK), are activated in PCOS and may potentiate the resistance to insulin since MAPK activity leads to phosphorylation of IRS-1 [92].

Oxidative stress, which is an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses favoring the former, is associated with a variety of pathological conditions including diabetes, cancer, and cardiovascular disease [93-95]. PCOS is also associated with increased oxidative stress and systemic inflammation [96-98]. Furthermore, antioxidant reserve appears to be compromised in women with PCOS [97]. Even lean women with PCOS exhibit increased oxidative stress, as measured by levels of malonyldialdehyde, a marker of lipid peroxidation, and they have decreased serum total antioxidant levels compared to controls [56]. Recent evidence suggests that inflammatory cytokines and measures of oxidative stress, such as tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) [99, 100], may play

a role in the dysregulation of the theca-interstitial compartment, and both of these factors are elevated in PCOS [97, 98, 101, 102].

ROS have a bimodal effect on theca cells such that modest oxidative stress stimulates proliferation of theca cells in vitro, while both greater oxidative stress and antioxidants, such as vitamin E succinate, inhibit their proliferation [100]. TNF-α and insulin also stimulate theca-interstitial cell proliferation [81, 82, 99]; furthermore, several in vitro and in vivo studies have shown that insulin and TNF-α also induce oxidative stress [103-105]. It is well known that ROS mediate proliferation of various other cell types, including fibroblasts and aortic endothelial cells [106], while antioxidants, such as vitamin E succinate, inhibit proliferation of vascular smooth muscle, fibroblasts, and many cancer cell lines [107-110].

In addition to simulating proliferation of theca-interstitial cells, moderate oxidative stress also induces testosterone and progesterone production by enhancing thecal expression of key steroidogenic enzymes, such as CYP17, CYP11A1, and 3βHSD [111]. Thus, the excess androgen production in PCOS is not only due to increased numbers of theca cells, but also to an induction of their steroidogenic capacity. Furthermore, oxidative stress, as discussed above, impairs insulin signaling, resulting in a compensatory hyperinsulinemia, which, in turn, further stimulates thecal steroidogenesis [89, 90]. Another significant result of oxidative stress is endothelial dysfunction and the subsequent development of cardiovascular disease [112].

Thus, the pathophysiology of PCOS involves oxidative stress with systemic inflammation and insulin resistance with resulting hyperinsulinemia, which promote dysregulation of the ovarian thecal compartment and dysfunction of endothelial cells, such that hyperandrogenism, anovulation, and cardiovascular disorders ensue (Figure 2). Given the significant sequelae of PCOS, prompt and effective treatment is warranted over the long term. The standard medical management of PCOS was recently reviewed [113] and will not be addressed here. Rather, the remainder of this review will focus on the rationale and evidence for the potential use of statins in the treatment of PCOS.

Statins

Statins are selective inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway. Statins improve the lipid profile primarily by decreasing total cholesterol and LDL levels [114, 115]. It has been well established that these medications significantly reduce both non-fatal and fatal cardiovascular disease events in primary and secondary prevention trials and thereby decrease cardiovascular morbidity and mortality [114-117].

In order to understand the potential role of statins in the treatment of PCOS, it is essential to review how statins affect the mevalonate pathway (Figure 3). This pathway consists of the reactions starting from acetyl-coenzyme A (acetyl-CoA) and leads to the formation of farnesyl pyrophosphate (FPP), which then serves as the substrate for several biologically important agents, including cholesterol, isoprenylated proteins, coenzyme Q, and dolichol [118, 119]. Particularly relevant to PCOS are the dolichols, which mediate the maturation of the insulin and Type 1 IGF-1 receptors [120], and cholesterol, which serves as the substrate for steroid hormones.

In addition to serving as a substrate for downstream products in the mevalonate pathway, FPP mediates the post-translational modification of other proteins, a process known as isoprenylation [#31]. Isoprenylation is required for membrane attachment and function of several families of proteins, including Ras and Ras-related GTP binding proteins (small GTPases) and protein kinases [121]. Specifically essential are members of the Ras superfamily, which include Ras, Rho, Rac, and Cdc 42. The functions of these proteins depend on their

association with the cytoplasmic leaflet of cellular membranes, a process that requires isoprenylation [121]. Since these small GTPases modulate proliferation, apoptosis, and function of cells, any interference with isoprenylation may have profound effects.

Interestingly, the effects of the mevalonate pathway correlate with several sites of insulin action as insulin increases ovarian steroidogenesis, protein isoprenylation, and ovarian theca-interstitial cell proliferation [83, 122-125]. Insulin simulates the phosphorylation and activation of farnesyl transferase [122, 123, 126-128], thereby augmenting the isoprenylation of Ras and other small GTPases [122-124, 129]. This leads to cellular proliferation by activation of the MAPK pathway, which is mediated by the small GTPases and their downstream effectors, such as Ras-Raf-extracellular signal-regulated kinase 1/2 (Erk 1/2).

Dolichol, a product of the mevalonate pathway, is required for the maturation of insulin and Type 1 IGF-I receptors [120]. Specifically, dolichol acts as a carbohydrate donor during N-linked glycosylation of membrane-targeted proteins [130]. While this post-translational modification is not critical for most cell surface receptors, the Type 1 IGF and insulin receptors require glycosylation for proper proreceptor cleavage, without which the proreceptor is retained within the endoplasmic reticulum [131, 132]; thus dolichol is essential for insulin and IGF-I signaling.

The mevalonate pathway also mediates the effects of oxidative stress, which shares some signal transduction pathways with insulin and IGF-I, specifically the Erk 1/2 and p70s6K pathways [133]. A convergence of the actions of insulin/IGF-I and ROS at the Erk1/2 and p70s6K pathways may explain the comparable effects of these agents on proliferation. Furthermore, ROS production by NADPH oxidase depends on isoprenylation, as the assembly of this enzyme requires the presence of isoprenylated Rac at the plasma cell membrane [134]. Cytosolic components of NADPH oxidase p47phox and p67phox complex with Rac1 to induce NADPH oxidase activity [135]. Thus, disruption of isoprenylation can lead to profound disturbances in cellular function, including decreased generation of intracellular ROS.

Statins reversibly block the conversion of HMG-CoA to mevalonate by HMG-CoA reductase, and the resulting depletion of mevalonate leads to a decrease in FPP with a consequent decrease in isoprenylation. In addition, by decreasing FPP and subsequently dolichol synthesis, statins have an inhibitory effect on N-linked glycosylation [130] and therefore, insulin and Type 1 IGF-1 proreceptor cleavage may be impaired. In addition, statins possess both indirect and direct antioxidant activity [136]. The antioxidant actions of statins include inhibition of NADPH oxidase activity, preservation of relative levels of vitamins C and E, as well as inhibition of the uptake and generation of oxidized LDL [134, 137]. The intrinsic antioxidant activity of statins involves both anti-hydroxyl and anti-peroxyl radical activity [136]. In vivo, statins reduce plasma levels of nitrotyrosine and chlorotyrosine [138], and they also exert anti-inflammatory effects by lowering C-reactive protein levels and suppressing pro-inflammatory agents, such as TNF-α [139].

The effects of statins on ovarian function, specifically in women with PCOS, are likely to involve multiple pathways (Figure 4). Firstly, by directly inhibiting production of cholesterol, the substrate for testosterone, statins can improve hyperandrogenemia. Secondly, statins may limit actions of insulin and IGF-I on the ovary not only by decreasing N-linked glycosylation and thus, maturation of insulin and Type I IGF-I receptors, but also by decreasing isoprenylation of small GTPases, such as Ras and Rac, which mediate some pathways of insulin signaling. In this way, blockade of the mevalonate pathway by statins, can lead to an abrogation of the stimulatory effects of hyperinsulinemia on thecal proliferation and steroidogenesis. Similarly, statins can directly and indirectly block the oxidative stress- mediated increases in cellular proliferation, steroidogenesis, and insulin resistance. By inhibiting isoprenylation, ROS generation by NADPH oxidase can be reduced by statins. The decreased oxidative stress

along with statin-mediated improvement in lipid profile, can have a beneficial effect on the long-term cardiovascular morbidity and mortality associated with PCOS.

Evidence for statin actions in vitro

In vitro, the statin mevastatin inhibits the proliferation of theca-interstitial cells and also inhibits LH-stimulated production of both progesterone and testosterone through a mechanism that is independent of its effect on cell number [140]. The inhibitory effects of mevastatin on ovarian cell proliferation are consistent with previous reports regarding other mesenchymal cell types, including vascular smooth muscle [141-143], cardiomyocytes [144], and mesangial cells [145].

The effects of statins on ovarian steroidogenesis may be due to several mechanisms. Besides impairing the availability of the substrate cholesterol, statins also decrease the expression of several key enzymes involved in testosterone production including P450scc, P450c17, and 3βHSD as demonstrated in adrenocortical cells [146, 147], and similar findings have been observed in ovarian cells [148]. It has been established previously that oxidative stress increases the expression of these same steroidogenic enzymes in the ovary [111]. A major source of ROS is the enzyme NADPH oxidase, which is activated by various cytokines [149]. Mevastatin and simvastatin, in the presence of LH, inhibit the expression of p22phox, a membrane-bound subunit essential for function of NADPH oxidase in theca-interstitial cells [150]. The expression of another NADPH oxidase subunit p47phox, is also decreased by these statins [150].

In addition, mevastatin blocks basal and insulin-dependent activation of the MAP kinase pathway in vitro as measured by phosphorylation of Erk1/2, a downstream kinase [151]. A recent study demonstrated that the inhibitory effects of simvastatin on theca-interstitial cell proliferation are only partially explained by blocked isoprenylation, and proliferation of these cells is sensitive to diverse inhibitors of glycosylation [152]. Therefore, part of the inhibitory effects of statins on insulin-mediated proliferation may be due to inhibition of N-linked glycosylation secondary to blockade of dolichol production. While decreased insulin and IGF-1 signaling at the level of ovarian thecal and stromal cells may be beneficial, decreased insulin receptor function at the level of other target tissues, such as liver, muscle, and adipose, may have potential negative consequences in terms of glucose metabolism. However, there is no evidence to date that statins cause or exacerbate insulin resistance.

Mevastatin and insulin have opposite effects on two signal transduction pathways that modulate proliferation: insulin alone stimulates the phosphorylation of the MAP kinase Erk1/2, while mevastatin blocks both its basal and insulin-dependent activation [151]. In contrast, mevastatin has no effect on either basal or insulin-stimulated Akt/protein kinase B (PKB) phosphorylation in theca-interstitial cells [151]. The above findings underscore the potential therapeutic importance of selective inhibition of Erk1/2, but not Akt/PKB by statins, such that insulin-mediated cellular proliferation of the theca-interstitial compartment may be abrogated without significantly affecting insulin-dependent glucose uptake, a process that appears to rely mostly on the Akt/PKB pathway [153, 154].

Thus, as summarized in Figure 5, the in vitro studies on ovarian theca-interstitial cells demonstrate that statins decrease cell proliferation and testosterone production, inhibit the expression of steroidogenic enzymes, decrease expression of NADPH oxidase subunits, and block MAPK-dependent phosphorylation. Furthermore, the proliferation of these cells is sensitive to glycosylation, a post-translational modification blocked by statins. Taken together, these finding raise the possibility that the use of statins in women with PCOS could decrease thecal hyperplasia, hyperandrogenism, and oxidative stress.

Evidence for stain actions in clinical trials

Recently, a randomized, prospective clinical trial investigated the effects of simvastatin on women with PCOS [155] and was followed by a cross-over study evaluating the effects of simvastatin and a combined oral contraceptive pill (OCP) on PCOS [156]. Women with PCOS, as defined by the ESHRE criteria, were treated with simvastatin plus OCP or OCP alone. Testosterone levels declined more in the presence of statin compared to the OCP alone; furthermore hirsutism was slightly, but significantly, improved in the presence of statin, while there was a non-significant decrease in hirsutism in subjects receiving OCP alone. In contrast to the effects on testosterone, simvastatin had no effect on DHEAS levels, suggesting that the actions of statins are selective and may not alter adrenal steroidogenesis.

However, simvastatin did affect the hypothalamo-pituitary axis, since between the groups, there were distinctly different responses noted with respect to gonadotropin levels. LH levels decreased more in the presence of statin, and as FSH levels did not significantly change, the net effect was a reduction in the LH:FSH ratio. Neither of the treatments had a significant effect on body mass index (BMI). The improvements in testosterone and LH by statin were not mediated by improved insulin sensitivity as determined by fasting and post-glucose challenge levels of insulin and glucose. In fact, fasting insulin and fasting glucose levels as well as oral glucose tolerance test results were not significantly altered by either treatment. This finding points to the different pathways of insulin with respect to its actions on glucose transport and other cellular functions, such as cellular proliferation, as discussed earlier.

As expected, total cholesterol and LDL decreased in the statin group, while there were small increases in these parameters in the OCP group. There was a small, but significant increase in HDL in both groups, and triglyceride levels were not affected by simvastatin treatment, while they increased in the OCP group. The improvement of the lipid profile by simvastatin is of particular value in PCOS, a condition characterized by dyslipidemia and other cardiovascular risk factors. In addition, while CRP levels slightly increased in the OCP group, a significant decrease from baseline was observed in the statin group, and statin treatment produced a more pronounced decrease in soluble vascular cell adhesion molecule-1 (VCAM-1) levels compared to OCP's alone VCAM-1 is expressed by the vascular endothelium under pro-inflammatory conditions and appears to play a role in the pathogenesis of atherosclerosis by mediating adhesion of activated leukocytes to the vasculature [157]. Regulation of VCAM-1 expression represents one on the many pleiotropic effects of statins [158]. The effects of OCPs and simvastatin in women with PCOS are summarized in Table 1.

Taken together, these data suggest that the use of statins in women with PCOS is likely to ameliorate the hyperandrogemia and dysregulation of gonadotropins secretion and it will offer significant protection from long-term cardiovascular morbidity. One limitation of the above studies was the concomitant use of OCPs with statins due to the fact that statins are considered pregnancy category X. The potential teratogenicity of statins limits their use in women who are at risk of conceiving. Recently, the risk of statin use during pregnancy has been extensively reviewed, and the available evidence suggests that statins are not major teratogens; the actual risk for an exposed pregnancy is low [159]. Still, given the paucity of research on statin use during pregnancy, and the pleiotropic actions of statins on numerous cellular processes, caution must be exercised in using these medications in women of reproductive age.

Conclusions

Statins appear to be a promising new therapeutic option for the medical management of PCOS. Statins target not only the dyslipidemia frequently associated with this endocrinopathy, but also the underlying stimulation of thecal proliferation and steroidogenesis. Given that the

mechanisms of statin actions are diverse and address the oxidative stress, systemic inflammation and effects of insulin resistance/hyperinsulinemia associated with the pathophysiology of PCOS, it is likely that they will be useful medications for the treatment of PCOS.

Further clinical studies of statins, particularly in the absence of OCPs should shed additional light on the mechanism of actions of these drugs on PCOS. As the use of statins in the treatment of PCOS is in its infancy, there are still numerous unanswered questions such as: What are the long-term effects of statins on women of reproductive age? Are the effects of statins different among patients with different PCOS phenotypes; for example, those with hyperinsulinemia versus normoinsulinemia? Or those without hyperandrogenemia? Should statins be used in women with PCOS, who have normal lipid profiles? Can statins be used effectively in women with PCOS from different ethnic groups? Can statins restore ovulation?

Given the heterogeneity of PCOS and the fact that it affects women who may or may not be interested in conceiving, the medical management of PCOS requires individualized considerations and patient-specific therapies. Based on the available evidence, statins can be used in women with PCOS, who have dyslipidemia and are not at risk of conceiving. Further studies of this potentially promising therapy are needed before it can be recommended for routine clinical use.

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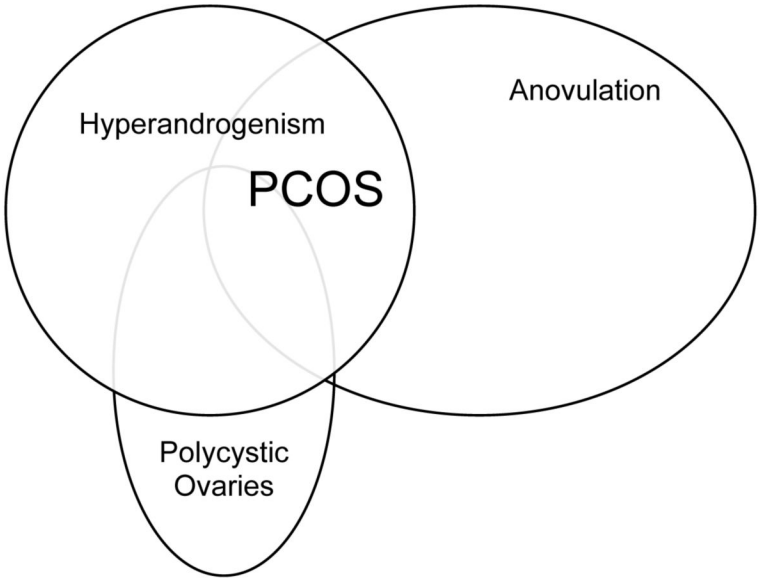

Fig. 1.
Diagram illustrating the criteria defining PCOS.
Criteria defining polycystic ovary syndrome (PCOS).

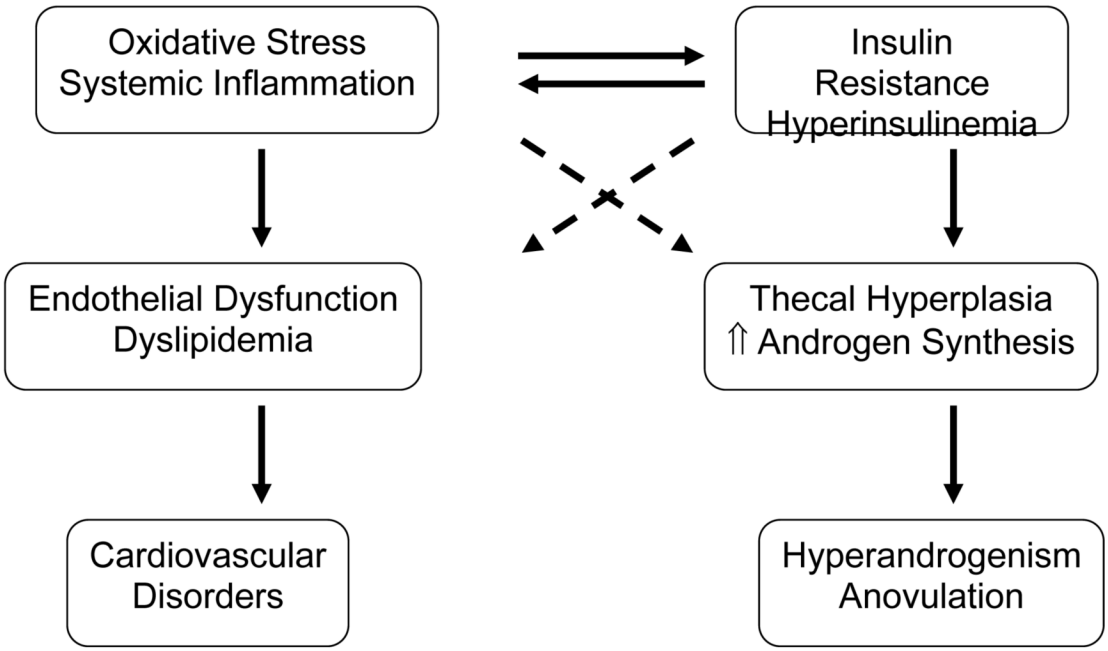

Fig. 2.

Proposed pathophysiology and sequelae of PCOS.

Proposed pathophysiology and sequelae of polycystic ovary syndrome. Oxidative stress with systemic inflammation and insulin resistance with resulting hyperinsulinaemia promote dysregulation of the ovarian thecal compartment and dysfunction of endothelial cells. Hyperandrogenism, anovulation and cardiovascular disorders ensue. ↑ indicates increased; solid line indicates estabilished cause and effect; dashed line indicates proposed pathway.

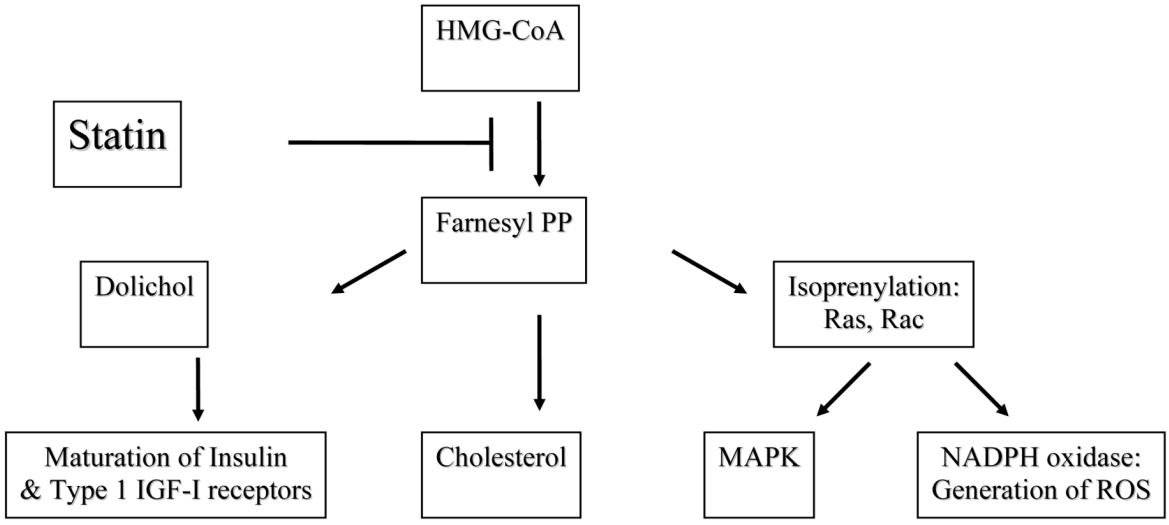

Fig. 3.

The mevalonate pathway and mechanism of statin action.

The mevalonate pathway and mechanism of HMG-CoA reductase inhibitor (statin) action. **IGF-I** = insulin-like growth factor I; **MAPK** = mitogen activated protein kinase; **NADPH** = nicotinamide adenosine dinucleotide phosphate; **PP** = pyrophosphate; **ROS** = reactive oxygen species

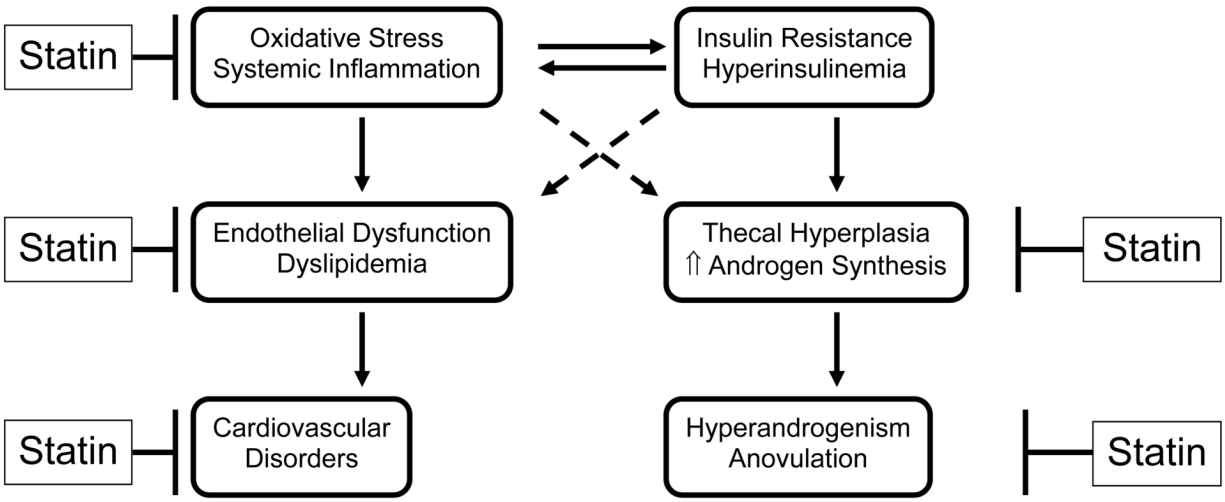

Fig. 4.

Rationale for the use of statins for treatment of PCOS.

Rationale for the use of HMG-CoA reductase inhibitors (statins) for the treatment of polycystic ovary syndrome. ↑ indicates increased; solid line indicates established cause and effect; dashed line indicates proposed pathway.

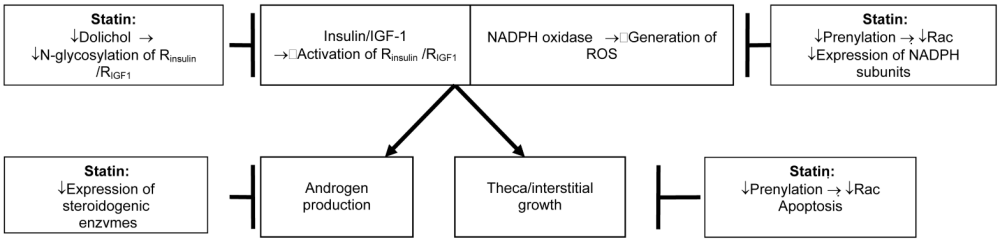

Figure 5.
Postulated effects of statins on ovarian theca-interstitial cells. Abbreviations: $R_{insulin}$, insulin receptor; R_{IGF1}, insulin-like growth factor 1 receptor.

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Table 1

Summary of effects of OCP and simvastatin. Data are presented as geometric means with 95% confidence intervals in parenthesis

Parameter	Baseline	OCP	Statin + OCP	Difference (Statin + OCP vs. OCP)	Effect of simvastatin (P-value)
Total Testosterone (ng/mL)	0.77 (0.69, 0.84)	0.57 * (0.51, 0.64)	0.48 * (0.43, 0.54)	−0.09 (−0.14, −0.03)	0.004
Free Testosterone (pg/ml)	1.20 (0.98, 1.48)	0.78 * (0.63, 0.97)	0.51 * (0.41, 0.64)	−0.27 (−0.40, −0.09)	0.006
DHEAS (μg/mL)	3.15 (2.77, 3.59)	2.22 * (1.99, 2.47)	2.27 * (2.03, 2.53)	0.05 (−0.20, 0.33)	0.70
SHBG (nmol/L)	64 (48, 79)	139 * (123, 155)	136 * (119, 152)	−3.4 (−16.9, 10.2)	0.62
LH (IU/L)	8.10 (6.74, 9.46)	6.62 * (5.78, 7.46)	5.07 * (4.20, 5.93)	−1.55 (−2.47, −0.63)	0.002
FSH (IU/L)	5.68 (5.21, 6.16)	6.32 * (5.78, 6.87)	6.01 (5.46, 6.57)	−0.31 (−0.91, 0.29)	0.30
LH:FSH ratio	1.27 (1.10, 1.46)	0.95 * (0.81, 1.10)	0.76 * (0.65, 0.89)	−0.19 (−0.30, −0.05)	0.01
Prolactin (ng/mL)	21.9 (19.1, 24.7)	23.1 (20.6, 25.6)	20.2 (17.5, 22.8)	−2.9 (−6.6, 0.7)	0.11
Hirsutism [1]	8.6 (7.3, 9.8)	8.2 * (8.0, 8.4)	7.9 * (7.6, 8.1)	−0.3 (−0.6, −0.1)	0.02
BMI (kg/m^2)	22.3 (21.3, 23.3)	22.3 (22.1, 22.6)	22.3 (22.1, 22.6)	0.0 (−0.2, 0.2)	0.99
Total Cholesterol (mg/dL)	190 (180, 201)	200 * (192, 207)	176 * (168, 184)	−24.0 (−34.6, −13.3)	<0.001
LDL Cholesterol (mg/dL)	107 (98, 115)	108 (101, 115)	85 * (77, 92)	−22.9 (−32.5, −13.4)	<0.001
HDL (mg/dL)	63 (59, 68)	70 * (67, 73)	72 * (69, 75)	1.8 (−1.1, 4.7)	0.22
Triglycerides (mg/dL)	86 (76, 96)	103 * (94, 113)	86 (78, 95)	−17.3 (−26.8, −6.7)	0.003
Fasting Insulin (μU/mL)	8.5 (7.3, 9.8)	9.4 (8.1, 10.6)	9.4 (8.1, 10.7)	0.04 (−1.40, 1.49)	0.95

Parameter	Baseline	OCP	Statin + OCP	Difference (Statin + OCP vs. OCP)	Effect of simvastatin (P-value)
Fasting Glucose (mg/dL)	85.2 (82.0, 88.4)	92.0 * (88.5, 95.5)	90.7 * (87.0, 94.3)	−1.3 (−5.7, 3.0)	0.55
Insulin AUC	47.0 (40.8, 54.0)	55.3 * (48.9, 62.6)	61.7 * (54.4, 70.0)	6.4 (−1.8, 15.9)	0.13
Glucose AUC	107 (101, 113)	113 * (107, 118)	112 (106,118)	−1.0 (−7.4, 5.4)	0.75
Insulin Sensitivity Index [2]	5.34 (4.62, 6.15)	4.54 * (3.97, 5.19)	4.16 * (3.63, 4.77)	−0.39 (−0.97, 0.30)	0.25
hs-CRP (mg/L) [3]	1.61 (1.08, 2.42)	1.70 (1.24, 2.34)	0.92 * (0.66, 1.29)	−0.78 (−1.10, −0.29)	0.006
sVCAM-1 (μg/L) [4]	583 (531, 640)	522 * (487, 559)	478 * (446, 513)	−44 (−740, −12)	0.01

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* Difference vs. baseline (P<0.05).

[1] Determined by Ferriman/Gallwey score

[2] Insulin Sensitivity Index determined as described by Matsuda and De Fronzo [1]

[3] hs-CRP: C-reactive protein

[4] sVCAM: soluble vascular cell adhesion molecule-1.