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Possible beneficial effect of statin in women with poly cystic ovarian syndrome (PCOs)

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A B S T R A C T

Background: Statins, as lipid-lowering agents are likely not only to improve the dyslipidaemia associated with polycystic ovary syndrome but may also exert other beneficial metabolic and endocrine effects. **Aim of the study:** Reviewing, assessing the possible beneficial effect of statins therapy in women with poly cystic ovarian syndrome conceive. **Search method:** Electronic searching of databases including published Cochrane library, Menstrual Disorders and Subfertility Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) , MEDLINE ,EMBASE , PubMed in English language up to February 2016 using the following keywords: Polycystic ovary syndrome, ovary polycystic disease, PCOS Statin, Atorvastatin, Simvastatin, Rosuvastatin, Lovastatin, Mevastatin, Pravastatin. **Inclusion Criteria:** randomised studies in which any statin was compared with placebo or other agent(s), or any statin in combination with another drug was compared to another class of drug alone in women with PCOS are included , non randomized controlled trials were excluded . **Data collection:** selecting trials that have the inclusion criteria from the search results , printed and collecting data from each study for results presented using , excluded studies that did not meet the inclusion criteria **Main results:** Four trials fulfilled the criteria for inclusion. They comprised a total of 244 women with PCOS receiving 12 weeks or 6 weeks of treatment. Two trials (184 women randomised) studied the effects of simvastatin and two trials (60 women randomised) studied the effects of atorvastatin. There was no good evidence that statins improved menstrual regularity, spontaneous ovulation rate, hirsutism or acne, either alone or in combination with the combined oral contraceptive pill (OCP). Nor were there any significant effects on body mass index (BMI). Statins were effective in lowering testosterone levels (nmol/L) (mean difference (MD) -0.90, 95% CI -1.18 to -0.62, $P < 0.00001$, 3 RCTs, 105 women) when used alone or with the OCP. Statins also improved total cholesterol, low-density lipoprotein (LDL) and triglycerides but had no significant effect on high-density lipoprotein (HDL) levels, high sensitivity (HS) Creactive protein (HS-CRP), fasting insulin or homeostatic model assessment (HOMA) insulin resistance. No serious adverse events were reported in any of the included studies. **Conclusions:** Statins are effective in improving the lipid profile of women with PCOS, Statins, either alone or with the oral contraceptive pill (OCP), also improve the biochemical parameter of hyperandrogenaemia (reducing the level of total testosterone) but There is no good evidence that statins improve menstrual regularity, ovulation rate, hirsutism or acne in women with polycystic ovary syndrome (PCOS), and there are no data on the long term safety of statins in women with PCOS, no data are available about the long-term cardiovascular risk profile in women with PCOS.

Keywords: Polycystic ovary syndrome, ovary polycystic disease, PCOS Statin, Atorvastatin, Simvastatin, Rosuvastatin, Lovastatin, Mevastatin, Pravastatin

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 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. 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.

Consequences of hyperandrogenism

Hyperandrogenemia or clinical manifestations of hyperandrogenism, such as hirsutism, malepattern 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].

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.

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 weightmatched 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.

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 [73,74]. 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 [73-76]

The effects of statins on ovarian function, specifically in women with PCOS, are likely to involve multiple pathways . 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.

AIM OF THE STUDY

Reviewing, assessing the possible beneficial effect of statins therapy in women with poly cystic ovarian syndrome.

METHODOLOGY

Search method

Electronic searching of databases including published Cochrane library, Menstrual Disorders and Subfertility Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) , MEDLINE ,EMBASE , PubMed in English language up to February 2016 using the following keywords:Polycystic ovary syndrome, ovary polycystic disease, PCOS Statin,Atorvastatin, Simvastatin, Rosuvastatin,Lovastatin,Mevastatin, Pravastatin

Inclusion Criteria

randomised studies in which any statin was compared with placebo or other agent(s), or any statin in combination with another drug was compared to another class of drug alone in women with PCOS are included , non randomized controlled trials were excluded .

Data collection

selecting trials that have the inclusion criteria from the search results , printed and collecting data from each study for results presented using , excluded studies that did not meet the inclusion criteria

RESULTS

four studies Were included (Duleba 2006; Banaszewska 2009; Sathyapalan 2009; Raja-Khan 2011), All the included studies were randomized controlled trials (RCTs).

Description of studies

1.Effects of atorvastatin on vascular function, inflammation, and androgens in women with polycystic ovary syndrome: a double blind, randomized placebo-controlled trial (Raja-Khan 2011)[77].

As LDL-cholesterol is the primary precursor for sex steroid biosynthesis, dyslipidemia may play a central role in the pathogenesis of polycystic ovary syndrome (PCOS), contributing to hyperandrogenemia and increased cardiovascular risk. Although many women with PCOS have dyslipidemia , they usually do not meet the National Cholesterol Education Program (NCEP) indications for statin therapy.

Beyond their LDL-lowering effects, statins inhibit ovarian theca-interstitial cell proliferation and steroidogenesis in vitro (4,5) and reduce T levels in women with PCOS (6–10). In non-PCOS populations, statins have been shown to reduce inflammation and cardiovascular events (11–13). In normocholesterolemic middle-aged men and patients with hypercholesterolemia, statins improve flow-mediated dilation (FMD), a non-invasive measure of endothelial function and early indicator of atherosclerosis (14–16). However, the effects of statins on FMD and other parameters of vascular function have not been investigated in PCOS.

The objective of this double-blind, randomized placebo-controlled trial was to determine whether atorvastatin improves brachial artery FMD and conductance, inflammation and hyperandrogenemia in PCOS.
The primary outcome was brachial artery FMD, the percent change in brachial artery diameter following release of transient occlusion.
The Institutional Review Board of Pennsylvania State University approved the study.
Written informed consent was obtained from all participants, the study was from October 20, 2006 to September 8, 2008, the inclusion criteria was Women with PCOS and LDL-cholesterol >100 mg/dl.
Twenty eligible women were randomized in a double-blind fashion to receive either atorvastatin 40 mg or placebo once daily for six weeks. At the end of the 6 weeks, measurements were repeated to assess change from baseline.
Randomization was performed according to Consolidated Standard of Reporting Trials (CONSORT) guidelines.
Results of the study : atorvastatin reduced androgen levels, biomarkers of inflammation, and blood pressure, increased insulin levels and brachial artery conductance during reactive hyperemia, and failed to improve brachial artery flow-mediated dilation.
The author conclude that until additional studies demonstrate a clear risk-to-benefit ratio favoring statin therapy in PCOS, statins should only be used in PCOS women who meet current indications for statin treatment, Appropriate contraception is required when statins are used in PCOS women with reproductive potential

2.The Effect of Atorvastatin in Patients with Polycystic Ovary Syndrome: A Randomized Double-Blind Placebo-Controlled Study (Sathyapalan 2009)[78].
Polycystic ovary syndrome (PCOS) is associated with increased risk of cardiovascular morbidity, whereas statins are proven to reduce cardiovascular mortality and morbidity through lipidloweringandperhaps through their pleiotropic effects. Statins can also reduce testosterone *in vitro* by inhibiting ovarian theca-interstitial cell proliferation and steroidogenesis and reducing inflammation *in vivo*.
Objective of the study was to assess the effect of atorvastatin on inflammatory markers, insulin resistance, and biochemical hyperandrogenemia in patients with PCOS.
Design of the study is a randomized, double-blind, placebo-controlled study at a tertiary care setting in United Kingdom.
The Patients included were 40 patients with PCOS and biochemical hyperandrogenemia.
Methods: Patients were randomized to either atorvastatin 20 mg daily or placebo.
Main Outcome Measures: The primary endpoint of the study was a change in the inflammatory marker high-sensitivity C-reactive protein. The secondary endpoints were a change in insulin resistance and total testosterone.
Results: After 12 wk atorvastatin, there was a significant reduction (mean_SEM) in total cholesterol (4.6_0.2 *vs.* 3.4_0.2 mmol/liter, *P*_0.01), low-density lipoprotein cholesterol (2.9_0.2 *vs.* 1.8_ 0.2 mmol/liter, *P* _ 0.01), triglycerides (1.34 _ 0.08 *vs.* 1.08 _ 0.13 mmol/liter, *P* _0.01), high sensitivity
C-reactive protein (4.9_1.4 *vs.* 3.4_1.1 mg/liter, *P*_0.04), free androgen index (13.4_0.6 *vs.* 8.7 _ 0.4, *P* _ 0.01), testosterone (4.1 _ 0.2 *vs.* 2.9 _ 0.1 nmol/liter, *P* _ 0.01) and insulin resistance as measured by homeostasis model assessment for insulin resistance (HOMA-IR) (3.3 _0.4 *vs.* 2.7 _ 0.4). There was a significant increase in SHBG (31.1 _ 1.0 *vs.* 35.3 _ 1.2 nmol/liter, *P* _0.01). There was a positive correlation between the reduction in HOMA-IR in the atorvastatin group with the reduction in triglycerides and

the reduction of free androgen index. There was a significant deterioration of HOMA-IR in the placebo group (3.0 _ 0.4 *vs.* 3.8 _ 0.5).
The author concluded that atorvastatin is effective in reducing inflammation, biochemical hyperandrogenemia, and metabolic parameters in patients with PCOS after a 12-wk period.

3.Simvastatin improves biochemical parameters in women with polycystic ovary syndrome: results of a prospective, randomized trial. (Antoni J. Duleba 2006)[79].

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies, affecting approximately 5%–7% of women of reproductive age, as observed in several unselected populations . Women with PCOS suffer from consequences of hyperandrogenism and anovulation, including hirsutism, infertility, and menstrual dysfunction. In the long term, they are at increased risk of adverse lipid profiles and hypertension, as well as cardiovascular or cerebrovascular morbidity . Polycystic ovary syndrome is also associated with increased oxidative stress and elevated markers of systemic inflammation, such as C-reactive protein .
Statins—3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors—have profound and broad-reaching biological effects . The competitive and reversible inhibition of HMG-CoA reductase by statins results in decreased hepatic cholesterol output and a compensatory increase in the expression of low-density lipoprotein (LDL) receptors in the liver . This mechanism plays a major role in binding and thus removing from circulation LDL and very-low-density lipoprotein (VLDL) particles, leading to reduction of total cholesterol, LDL cholesterol, and triglyceride levels. Furthermore, statins possess other cardioprotective properties, including antioxidant and anti-inflammatory actions .
Design of the study was Prospective, randomized trial.
Setting: Academic medical center.
Participants gave informed consent, approved by the Ethics Committee at Poznan University of Medical Sciences. The study was also approved by the Human Investigations Committee at Yale University School of Medicine
Inclusion criteria were: at least two of the three following criteria: [1] chronic anovulation, [2] hyperandrogenism (hirsutism, acne) and/or hyperandrogenemia (total T 75 ng/dL), and [3] polycystic ovaries.
Intervention(s)**:** Forty-eight women with PCOS were randomized to a statin group (simvastatin, 20 mg daily plus oral contraceptive pill [OCP]; n = 24) or an OCP group (OCP alone; n = 24).
The main Outcome Measure(s) was Serum T.
Result(s) : Baseline parameters of both groups were comparable. After 12 weeks of treatment, serum T levels declined by 41% in the statin group and by 14% in the OCP group. In the statin group, there was a greater decrease of LH (43% decrease vs. 9% in the OCP group) and a greater decline of LH/FSH ratio (44% vs. 12%). In the statin group, total cholesterol declined by 10% and low-density lipoprotein (LDL) by 24%. In the OCP group, total cholesterol increased by 8%, and LDL was unchanged.
the author concluded that statin decreases T levels and normalizes gonadotropin levels in women with PCOS. Statin therapy might offer a novel approach, providing endocrine and cardiovascular benefits.

4.Comparison of Simvastatin and Metformin in Treatment of Polycystic Ovary Syndrome: Prospective Randomized Trial (Beata Banaszewska 2009)[80].

Polycystic ovary syndrome (PCOS) is characterized by ovarian dysfunction and hyperandrogenism; it is also associated with increased cardiovascular risks such as adverse lipid profile and endothelial dysfunction. Metformin and, more recently, statins have been shown to improve endocrine and metabolic aspects of PCOS.

The aim of the study was to compare effects of simvastatin and metformin on PCOS.

Design: In a prospective trial, women with PCOS (n 136) were randomized to simvastatin (S), metformin (M), or simvastatin plus metformin (SM) groups.

PCOS was defined according to modified Rotterdam criteria: 1) the presence of clinical and/or biochemical signs of hyperandrogenism; and 2) at least one of the following: oligo- or anovulation and/or polycystic ovaries (20, 21). In all subjects, congenital adrenal hyperplasia was excluded by determination of normal morning follicular phase 17-hydroxyprogesterone (2 ng/ml), whereas hyperprolactinemia was excluded by determination of normal levels of prolactin. Cushing's syndrome and androgen-secreting tumors were excluded based on clinical presentation. None of the subjects had thyroid disease or diabetes mellitus. All recruited women had no history of cardiovascular disease and no hypertension. All patients had normal concentrations of bilirubin, aminotransferases, blood urea nitrogen, and creatinine. Polycystic ovaries were identified according to standard ultrasonographic criteria (22). Participants were recruited among patients evaluated for PCOS at Poznan University of Medical Sciences between December 2006 and March 2009; all participants gave informed consent, and the study was approved by the Institutional Review Board at the Poznan University ofMedical Sciences and the Institutional Review Board at the University of California Davis. The study was registered at clinicaltrials.gov with identifier NCT00396513. For at least 3 months before the study, all subjects refrained from the use of any form of oral contraceptives, other steroid hormones, or any other treatments likely to affect ovarian function, insulin sensitivity, or lipid profile.
Evaluations were performed at baseline and after 3 months.
Setting: The study was conducted at an academic medical center.
Primary Outcome: The change of serum total testosterone was measured.
Results: The study was completed by 113 subjects. Total testosterone decreased significantly and comparably in all groups: by 17.1, 13.6, and 15.1%, respectively, in the S, M, and SM groups. Significant decreases were also observed in all groups with respect to body mass index, C-reactive protein, and soluble vascular cell adhesion molecule-1. DHEAS declined significantly only in the S group. None of the treatments were associated with significant changes in LH or FSH. Total cholesterol and low-density lipoprotein cholesterol significantly declined only in S and SM groups.
Conclusions of the study is that Simvastatin treatment was superior to metformin alone, whereas a combination of simvastatin and metformin was not significantly superior to simvastatin alone.

DISCUSSION

Summary of main results

This review aimed to generate evidence on the efficacy and safety of statin for the treatment of the hyperandrogenaemia and adverse metabolic parameters of polycystic

ovary syndrome (PCOS) in women not attempting to conceive. There were a limited number of studies for inclusion in the meta-analyses. After six weeks to 12 weeks of treatment, there were no evidence of effect of statins alone or statins in combination with the oral contraceptive pill (OCP) on clinical outcomes like resumption of menstrual regularity, resumption of spontaneous ovulation, hirsutism and acne. However in terms of biochemical parameters, statins or statins combined with either the OCP or metformin in women with PCOS leads to a reduction in serum testosterone level, a surrogate indicator of clinical outcomes for hirsutism or acne. As
expected we found that statin alone or in combination with OCP significantly reduced total cholesterol, LDL and triglyceride levels, which are the surrogate markers for cardiovascular outcomes.
However no evidence of effect for statin alone or with OCP on HDL. also no evidence of effect of statin alone or combination with OCP on fasting insulin, HS C-reactive protein (HS-CRP) or insulin resistance (HOMA-IR). This may limit the usefulness of statin in hyperinsulinaemia or metabolic syndrome in women with PCOS. In addition, we found no evidence founded about any effect of statins alone or with OCP on the improvement of waist circumference or BMI. Hence, statins are not indicated for weight reduction in women with PCOS.
The side effect profiles were mild to moderate with no serious adverse drug events reported.Minor side effects were not reported in detail. All the studies were of short duration (threemonths) and long-term data on the comparative effects of statins are lacking for important clinical outcomes such as resumption of menstrual
regularity.

Overall completeness and applicability of evidence

In all the studies populations were well defined and there was a clear definition of PCOS.There was a difference with respect to bodymass index (BMI) and serum insulin levels between the included studies at baseline. The participants in Duleba 2006 had a normal BMI and more than 50% of patients in the OCP group had a serum testosterone level less than 80 ng/dl and an insulin level less than 15 μIU/l. Sathyapalan 2009 and Raja-Khan 2011 had (relatively) very obese women with high insulin levels.
Most of the data in this review are derived from women with PCOS who were recruited from European and US centres. This may limit the potential applicability of the results of this review if ethnic variation affects the risk of adverse outcomes (clinical or metabolic) or responses to statin therapy. There are a limited number of randomised controlled trials (RCTs) comparing statin versus placebo or statin combined with another drug versus the other drug alone. Another factor that may limit the applicability of this review is that the sample size of the included studies was small. A number of the results are constrained by wide confidence intervals, which limit the precision and confidence of conclusions. Some of the planned analyses could not be performed due to the limited number of studies.
Sathyapalan 2009 reported no changes in the length of the menstrual cycle associated with the use of statins alone. The Ferriman-Gallwey scale for assessment of hirsutism was used in most of the included studies. None showed evidence of improvement in Ferriman-Gallwey scale with statin, alone or in combination.
Two of the studies focused on testosterone as a primary outcome.It is founded that statins are effective in reducing total testosterone.
There are insufficient studies to date assessing whether this more favourable biochemical androgen profile leads to a more favourable clinical androgen effect in terms of hirsutism or acne.

No significant effect of statin on HS-CRP was observed. No serious adverse events were reported. No or limited data are available to confirm the safety profile of statins in young women with PCOS in the long term. They are potentially teratogenic so are not recommended for women who are intending to conceive.
None of the studies mentioned the time of administration of statin. Statin administration time is also one crucial factor for the efficacy of certain statins as there are sufficient data to support evening administration of simvastatin to achieve optimal lowering of LDLC levels [81].

CONCLUSIONS

Statins are effective in improving the lipid profile of women with PCOS, which ultimately may lead to beneficial effects in treating parameters of the metabolic syndrome associated with PCOS. Statins, either alone or with the oral
contraceptive pill (OCP), also improve the biochemical parameter
of hyperandrogenaemia (reducing the level of total testosterone) but There is no good evidence that statins improve menstrual regularity,ovulation rate, hirsutism or acne in women with polycys-tic ovary syndrome (PCOS), and there are no data on the long term safety of statins in women with PCOS, no data are available about the long-term cardiovascular risk profile in women with PCOS.

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