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STATINS IN POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women. PCOS varies from a mild menstrual disorder to severe disturbance of reproductive and metabolic functions. Statins, 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors with intrinsic antioxidant properties, exert profound and broad-reaching effects on various types of tissues. By blocking an early step of the mevalonate pathway, statins inhibit proliferation of several cell types including vascular smooth muscles, hepatocytes, and several neoplastic cell lines. The pleiotropic effects of statins may be due to inhibition of cholesterol synthesis. Some common treatments lifestyle changes, insulin-sensitizing agents.

INTRODUCTION: Polycystic ovaries are slightly larger than normal ovaries and have twice the number of follicles (small cysts). Polycystic ovaries are very common affecting 20 in 100 (20%) of women. PCOS is a form of hyperandrogenism in which hormonal imbalances cause the ovaries to overproduce androgens. It is a common cause of hirsutism and is frequently associated with irregular or absent ovulation and infertility. In patients with PCOS, multiple small cysts develop in the ovaries, hence the term "poly-cystic **(Figure 1).**

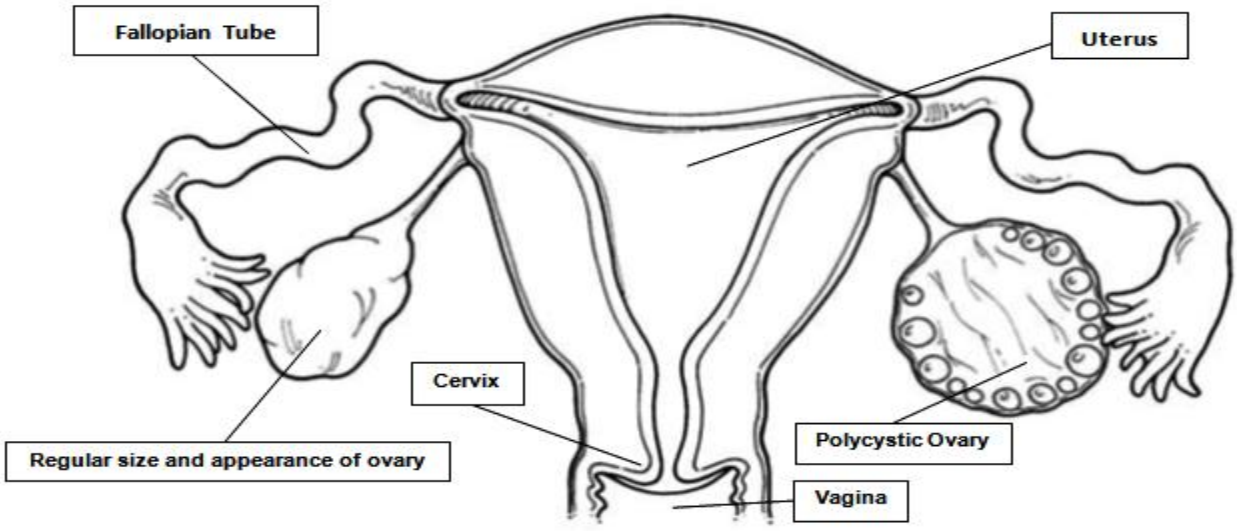

FIG. 1: THE POLYCYSTIC OVARY MAY BECOM ENLARGED WITH MANY SMALL CYSTS

Polycystic ovarian syndrome is the most common cause of an ovulatory infertility [1]. It affects 5-10% of women in the reproductive age group [2]. The disease is characterized by ovarian dysfunction, androgen excess and multiple cysts in the ovary. Clinically patients may present with oligomenorhoea, amenorrhea, infertility, hirsuitism, acne & obesity. Women with this syndrome have at least seven times the risk of myocardial infarction and ischemic heart disease than other woman, and by the age of 40 years up to 40% will have type -II diabetes or impaired glucose tolerance [3, 4].

The definition of polycystic ovary syndrome (PCOS) has evolved over the past several years [5, 6]. PCOS was originally described in 1935 by Irving Stein and Michael Leventhal [7] who reported a group of women with amenorrhea and polycystic ovaries, of which some were hirsute and/or obese. In 1990, a National Institutes of Health (NIH) consensus conference defined PCOS as a combination of hyperandrogenism, menstrual dysfunction (oligo and/or anovulation), and exclusion of known disorders such as PCOS congenital adrenal hyperplasia (CAH) leading to the above [8]. Current estimates suggest that affects 5–10% of reproductive age women [9-12].

Obesity is a common finding in women with PCOS. Young women with polycystic ovary syndrome (PCOS) present a high risk for cardiovascular disease because of the presence of abdominal obesity, insulin resistance and excess androgen. The impact of statins on other common features of PCOS, This may be relatively more important given the overall concerns of young women with PCOS, who experience irregular cycles and hirsutism as key features of the disease. Statins not only improve lipid profile, but also exert a broad range of other cardioprotective effects, including anti-inflammatory properties and improved endothelial function [13-16].

Pathophysiology: The etiology of PCOS remains controversial and many factors play a role in development and disease progression[14]. Data are accumulating that PCOS is a complex trait with contributions from both heritable and environmental factors [6, 15]. Multiple studies have documented a familial incidence reflecting a genetic predisposition, but the exact role of genes in the pathogenesis has not been elucidated [16]. In addition, many patients with PCOS have a family history of type 2 diabetes.

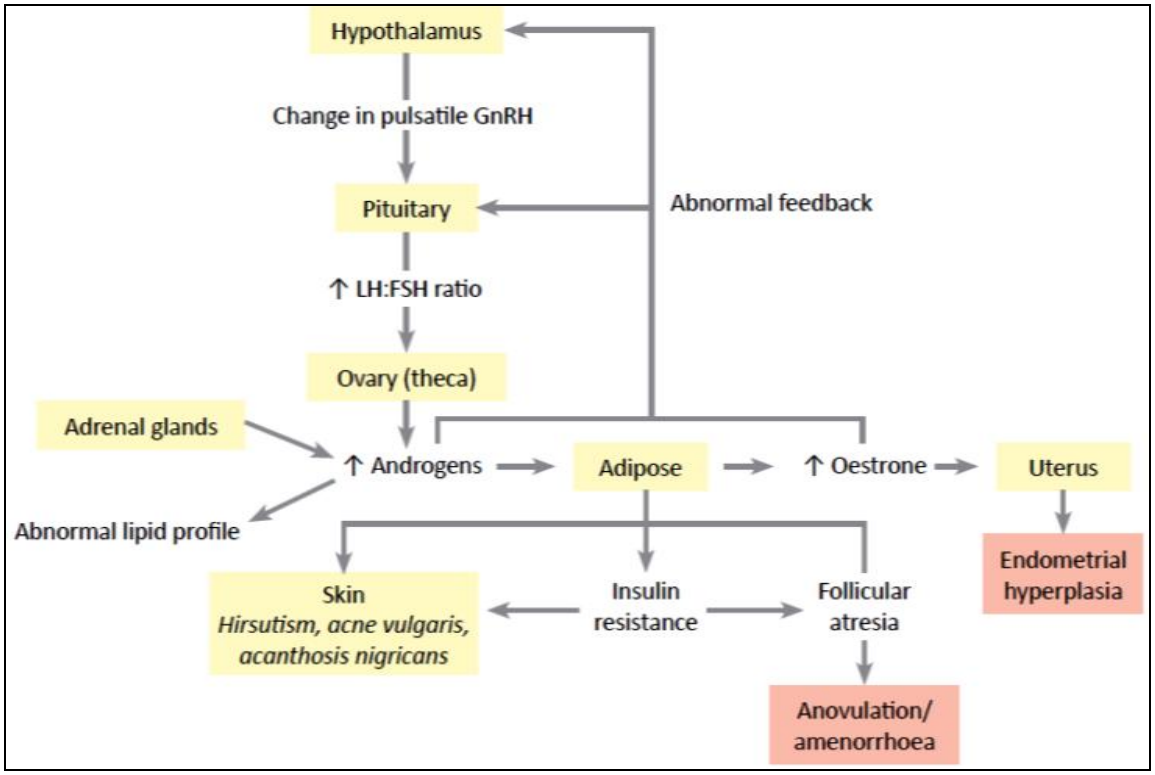

FIG. 2: THE FLOW CHART ABOVE DETAILS THE SUGGESTED PATHOPHYSIOLOGY OF POLYCYSTIC OVARY SYNDROME. ENDOCRINE ABNORMALITIES ARE THOUGHT TO OCCUR AT THE LEVEL OF THE HYPOTHALAMUS, PITUITARY AND OVARY. PCOS THEN MANIFESTS ITSELF IN THE PRESENCE OF INSULIN RESISTANCE DUE TO THE PRESENCE OF EXCESS ADIPOSE TISSUE. INSULIN RESISTANCE CONTRIBUTES TO AN OVULATORY INFERTILITY AND AMENORRHOEA IN AFFECTED WOMEN

Women with PCOS, both lean and obese, may be insulin resistant as reflected by accompanying hyperinsulinemia [17]. In addition to affecting glucose metabolism, insulin may also lead to increased circulating androgen levels by stimulating ovarian androgen secretion [10-18]. High insulin levels decrease liver production of sex hormone binding globulin, leading to increasing levels of free testosterone and worsening signs of hyperandrogenism [19]. Increased androgens are responsible not only for hirsutism and acne, but also play a role in promoting abnormal follicular development leading to menstrual disturbances and the development of central obesity.

The presence of central obesity may aggravate insulin resistance, further worsening the hormonal imbalances [20]. In addition, it is thought that accelerated gonadotropin releasing hormone (GnRH) pulse activity results in an exaggerated release of luteinizing hormone (LH) [21]. Even a mild, chronic elevation in LH can blunt the effect of the hormone surge, leading to anovulation. LH may act synergistically with insulin in stimulating the ovary to secrete testosterone [10, 19, 22].

The spectrum of irregular menses, estimated to be present in about 66% of adolescents with PCOS [23-27], includes primary or secondary amenorrhea, oligomenorrhea, anovulatory regular menses and dysfunctional uterine bleeding with oligomenorrhea most common. The associated obesity typically involves a central distribution of fat, with an increased waist to hip ratio and increased visceral fat [10].

In addition to obesity, acanthosis nigricans, a velvety rash on the neck, maxilla and groin, is a clinical sign of hyperinsulinism. Unfortunately, many of the above symptoms may be attributed to normal pubertal development, thus delaying the diagnosis. While some adolescents do have transient androgen excess and irregular menses and should not be prematurely given the label of PCOS, the symptoms and signs of PCOS should be carefully assessed, particularly in those with a family history of PCOS and/or type 2 diabetes.

Symptoms: Polycystic ovary syndrome signs and symptoms often begin soon after a woman first begins having periods (menarche). In some cases, PCOS develops later on during the reproductive years, for instance, in response to substantial weight gain**.**

Signs and symptoms vary from person to person, in both type and severity. To be diagnosed with the condition, doctor looks for at least two of the following:

Menstrual abnormality is the most common characteristic and it includes menstrual intervals longer than 35 days; fewer than eight menstrual cycles a year; failure to menstruate for four months or longer; and prolonged periods that may be scant or heavy.

Excess androgen may result in physical signs, such as excess facial and body hair (hirsutism), adult acne or severe adolescent acne, and male-pattern baldness (androgenic alopecia). Polycystic ovaries are enlarged ovaries containing numerous small cysts can be detected by ultrasound. Despite the condition's name, polycystic ovaries alone do not confirm the diagnosis. To be diagnosed with PCOS, women must have abnormal menstrual cycles or signs of androgen excess. Some women with polycystic ovaries may not have PCOS, while a few women with the condition have ovaries that appear normal.

A woman who has two of the following features may be diagnosed with PCOS [24]. Absence of ovulation that leads to menstrual irregularities and high levels of androgens that do not result from other causes or conditions. Women who are diagnosed with PCOS may have symptoms of PCOS, but no cysts on their ovaries. Similarly, some women have cysts on their ovaries but no symptoms of PCOS.

Treatments: Some common treatments for PCOS targets decreasing the effects of high androgen levels (for example, those with irregular periods, acne, or hirsutism) include the following: Lifestyle changes therapy and possibly insulin sensitizers are associated with improvement in ovulatory function.

Lifestyle changes should focus on weight loss as well as lifestyle modifications to improve insulin sensitivity, prevent impaired glucose tolerance and diabetes in obese or overweight patients. Dietary intervention studies have consistently shown that weight reduction can reduce androgen levels and improve menstrual function [28], as well as reduce insulin concentrations [29]. As little as a 5–7% decrease in body weight has been shown to decrease testosterone levels and lead to resumption of menses [12, 30, 31].

Simple dietary modifications that involve eating a well-balanced diet with restriction of caloric intake and portion size should be combined with regular, moderate exercise. Unfortunately many teenagers find it difficult to implement these recommendations. Obese women with PCOS also tend to have a harder time losing weight despite lifestyle interventions and have difficulty maintaining a healthy weight [10, 32]. Although making these interventions as a first step, many adolescents with PCOS require pharmacological intervention, including those who are lean, and therefore for whom weight loss is not a beneficial therapeutic option.

Insulin-sensitizing agents make body more sensitive to the available insulin as a way to help cells better use blood glucose. Studies reported that short-term use of insulin sensitizers effectively [33] regulates menstrual periods and ovulation, reduces infertility associated with PCOS, minimizes the signs of hirsutism [34] as well as reduces acne. Better use of insulin in the body also decreases the risk of cardiovascular disease and diabetes, which both are common in women with PCOS than normal [35]. Currently, the U.S. Food and Drug Administration (FDA) have not approved these medications specifically for the treatment of PCOS symptoms. However, health care provider may still use these agents to treat symptoms of PCOS.

Ovulation inducing drug clomiphene citrate is used for the treatment of infertility. By inhibiting the estrogen mediated negative feedback loop of hypothalamus, it enhances secretion of F.S.H. (follicle stimulating hormone). But it carries an increased risk of multiple pregnancies. Also due to potential risk of ovarian cancer, it should not be continued more than 6 months [36]. Those failing to conceive after clomiphene treatment usually respond to exogenous gonadotrophin, but this is expensive, not available, needs special care during therapy and is burdened with the risk of multiple pregnancies.

Statins: The newest addition to PCOS treatment options are the statins. It has long been hypothesized that statins would be beneficial in PCOS treatment because of their effect in reducing sex steroid production and improving dyslipidemia. Polycystic ovary syndrome is associated with increased risk of cardiovascular morbidity, whereas statins are proven to reduce cardiovascular mortality and morbidity through lipid lowering and perhaps through their pleiotropic effects. In vitro studies have shown that statins may also reduce ovarian androgen production by inhibiting proliferation and androgen production of theca-interstitial cells [37-39].

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl- coenzyme A reductase, a rate-limiting step of the mevalonate pathway. The pleiotropic effects of statins may be due to inhibition of cholesterol synthesis, as well as decreased availability of several biologically important intermediate components of the mevalonate pathway. 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.

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 [40, 41]. Particularly relevant to PCOS are the dolichols, which mediate the maturation of the insulin and Type 1 IGF-1 receptors [42], and cholesterol, which serves as the substrate for steroid hormones.

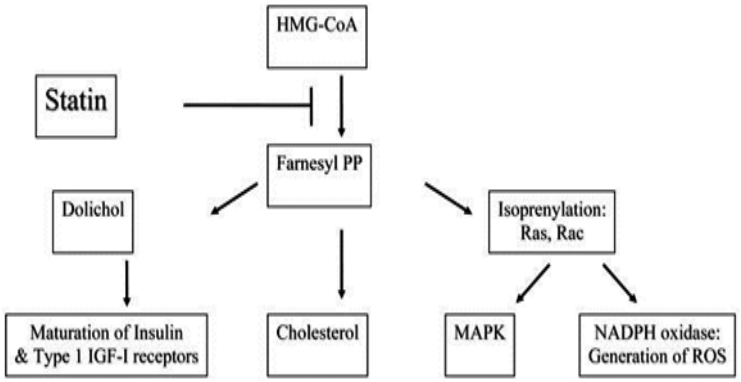

FIG. 3: THE MEVALONATE PATHWAY AND MECHANISM OF HMG-COA REDUCTASE INHIBITOR (STATIN) ACTION. IGF-I = INSULIN-LIKE GROWTH FACTOR I; MAPK= MITOGEN ACTIVATED PROTEIN KINASE; NADPH = NICOTINAMIDE ADENOSINE DINUCLEOTIDE PHOSPHATE; PP = PYROPHOSPHATE; ROS = REACTIVE OXYGEN SPECIES

In addition to serving as a substrate for downstream products in the mevalonate pathway, FPP (farnesyl pyrophosphate) mediates the post-translational modification of other proteins, a process known as isoprenylation. Isoprenylation is required for

membrane attachment and function of several families of proteins, including ras and ras-related GTP (guanosine triphoshphate) binding proteins (small GTPases) and protein kinases [43].

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[44-47]. Insulin stimulates the phosphorylation and activation of farnesyl transferase[44, 45], thereby augmenting the isoprenylation of ras and other small GTPases [44, 46].

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 increase cellular proliferation, steroidogenesis and insulin resistance. By inhibiting isoprenylation, ROS (reactive oxygen species) generation by NADPH (nicotinamide adenosine dinucleotide phosphate) 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.

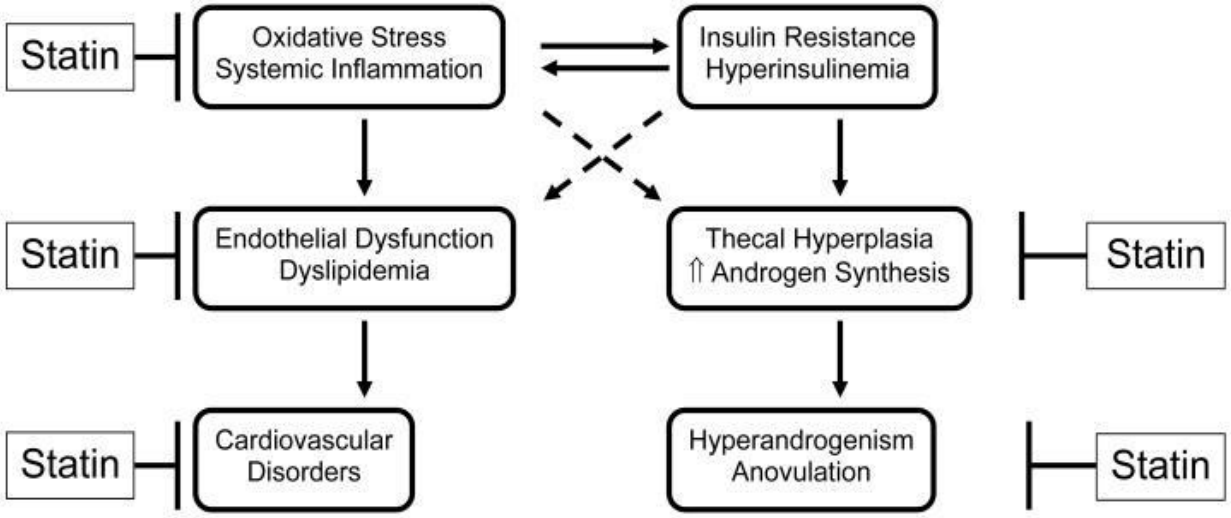

FIG. 4: RATIONALE FOR THE USE OF HMG-COA REDUCTASE INHIBITORS (STATINS) CAUSE AND EFFECT; DASHED LINE INDICATES PROPOSED PATHWAY FOR THE TREATMENT OF POLYCYSTIC OVARY SYNDROME. ↑ INDICATES INCREASED; SOLID LINE INDICATES ESTABLISHED

Evidence for statin action *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 [48]. The inhibitory effects of mevastatin on ovarian cell proliferation are consistent with previous reports regarding other mesenchymal cell types, including vascular smooth muscle [49], cardiomyocytes [50], and mesangial cells [51].

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 [52, 53], and similar findings have been observed in ovarian cells. It has been established previously that oxidative stress increases the expression of these same steroidogenic enzymes in the ovary [54].

A major source of ROS is the enzyme NADPH oxidase, which is activated by various cytokines [55]. 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 [56]. The expression of another NADPH oxidase subunit p47phox, is also decreased by these statins [56].

In addition, mevastatin blocks basal and insulin-dependent activation of the MAP (mitogen activated protein) kinase pathway in vitro as measured by phosphorylation. 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 [57]. 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.

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(mitogen activated protein kinase)-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 (Fig. 5).

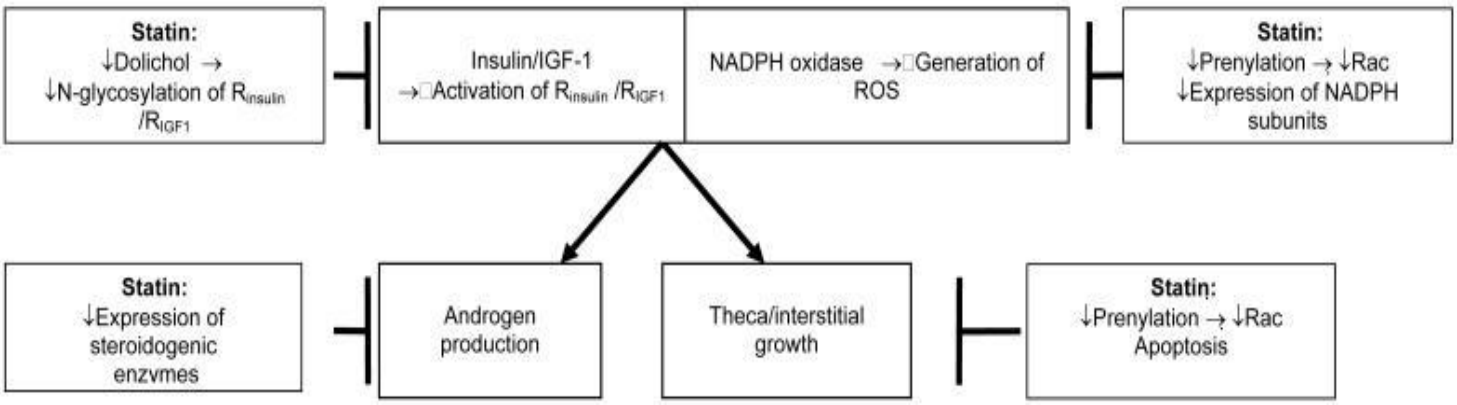

FIG. 5:

Evidence for statin in Clinical Trial: Recently, a randomized, prospective clinical trial investigated the effects of simvastatin on women with PCOS [58] and was followed by a cross-over study evaluating the effects of simvastatin and a combined oral contraceptive pill (OCP) on PCOS [59]. Women with PCOS, as defined by the ESHRE (European Society of Human Reproduction and Embryology) 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 (dihydroepininoandrosterone) 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 (luteinizing hormone) 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 expected, total cholesterol and LDL (Low-density lipoprotein) 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 (high-density lipoprotein) 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(C- reactive protein) 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 [60]. Regulation of VCAM-1 expression represents one on the many pleiotropic effects of statins.

Atorvastatin induced a significant decrease of testosterone, C-reactive protein, and insulin resistance, as well as improvement of lipid profile[61].

The common side effects of statins are headache, nausea, vomiting, constipation, diarrhea, rash, weakness and muscle pain. While the most serious side effects are liver failure and rhabdomyolysis.

CONCLUSION: Many women of reproductive age are affected by polycystic ovary syndrome (PCOS), a heterogeneous endocrinopathy characterized by androgen excess, chronic oligo-anovulation. Evidence of statins, both *in vitro* and *in vivo*, suggests that statins have potential in the treatment of PCOS. A recent randomized prospective clinical trial evaluated the effects of simvastatin on women with PCOS. Simvastatin treatment reduced serum testosterone, normalized gonadotropins, and improved lipid profile. In summary, inhibition of the mevalonate pathway by statins profoundly affects function and growth of ovarian mesenchyme and may result in both improved ovarian function and systemic cardiovascular benefits in women with PCOS. Statins offer a novel therapeutic approach to PCOS in that they address the dyslipidaemia associated with the syndrome, as well as hyperandrogenism or hyperandrogenaemia. These actions may be due to an inhibition of the effects of systemic inflammation and insulin resistance.

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