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# THE EFFECT OF ATORVASTATIN VERSUS METFORMIN ON THE CLINICAL AND BIOCHEMICAL HYPERANDROGENISM IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

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**ABSTRACT**

Background*:* polycystic ovary syndrome (PCOS) is the most common endocrine-metabolic disease affecting 5-10% of women in reproductive age characterized by hyperandrogenaemia, hirsutism, oligo- or amenorrhoea and anovulation. PCOS is frequently associated with hyperinsulinaemia, insulin resistance syndrome, increased cardiovascular risk and diabetes mellitus. Today various classes of drugs being used in PCOS women with various benefit. This study aimed to compare efficacy of metformin and atorvastatin and their combination on clinical and biochemical hyperandrogenism in women with PCOS. Subjects and methods: a randomized, open labeled clinical study was conducted at Al- Basra Hospital for Maternity and children; one hundred and eight women with PCOS were enrolled while attending the outpatient clinic of Gynecology the mean age of women (28.31 ± 0.51) and mean body mass index (BMI) (26.64 ± 0.28)) , in addition we recruited forty five healthy women matched for age and BMI as control. Women with PCOS were randomly divided in to three groups: group I (given metformin 850 mg twice daily), group II (given atorvastatin 20 mg daily) and group III (given combination of metformin and atorvastatin). Change in clinical and biochemical variable where measured and compared at base line and after three months of treatment. Results*:* after three months of treatment, the using combination metformin plus atorvastatin appear to be superior to use any drug alone as indicated by significant improvement in all clinical and biochemical parameters of hyperandrogenism in group III as compared to their base line and group I and II values (body mass index(BMI), scoring of hirsutism, acne score, serum levels of total and free testosterone, sex hormone binding globulin (SHBG), androstenedione, dehydroepiandrosterone sulfate (DHEAS) and free androgen index (FAI )). In group II there was significant improvement in all parameters in exception to BMI, hirsutism and acne score, where there was no significant changes in these parameter after three months of treatment. While in group I there was improvement only in total and free testosterone, SHBG, FAI with no significant changes in all other parameters. Conclusions: the use of atorvastatin in women with PCOS will improve hyperandrogenism better than do metformin, using combination of metformin and atorvastatin will represent a novel combination to improve clinical and biochemical hyperandrogenism in women with PCOS.

**KEYWORDS:** Polycystic ovary syndrome, metformin, atorvastatin and hyperandrogenism.

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common and heterogeneous syndrome associated with a wide range of clinical, hormonal, and metabolic abnormalities affecting 5–10% of women of reproductive age[1,2]. Depending on the population being examined, however, prevalence rates as high as 26% have been reported [3]. It has been estimated that the total cost of evaluating and providing care to reproductive- aged PCOS women in the United States exceeds 4 $ billion annually[4]. Although debate on what constitutes PCOS continues, the Rotterdam Consensus on Diagnostic Criteria for PCOS published in 2003 is the most current definition. According to this consensus, a diagnosis of PCOS is based on at least 2 of the following 3 criteria: oligo-ovulation or anovulation, clinical or biochemical evidence of hyperandrogenism, and polycystic ovaries on ultrasound assessment (> 12 small antral follicles in an ovary), with the exclusion of medical conditions such as congenital adrenal hyperplasia, androgen-secreting tumours, or Cushing's syndrome.[5]

The signs and symptoms associated with this condition are menstrual cycle disturbances, obesity, infertility, acne, hirsutism and other signs of hyperandrogenism, and polycystic ovary (PCO) morphology on transvaginal ultrasound scan[6]. Metabolic disturbances such as elevated serum concentrations of luteinizing hormone (LH), testosterone (T), insulin and prolactin are often present and these may have profound implications on the long-term health of women with PCOS[7].

More recently it has become apparent that this syndrome is also linked to a broad range of cardiovascular risk factors. In particular, women with PCOS are at increased risk for dyslipidemia, hypertension, insulin resistance, gestational and type 2 diabetes, systemic inflammation, endothelial dysfunction, and ultimately, cardiovascular morbidity[8,9,10,11]. Hyperandrogenemia or clinical manifestations of hyperandrogenism, such as hirsutism, male pattern balding, and acne, are common among women with PCOS[12]. Androgen excess may contribute to the cardiovascular risks associated with PCOS. For instance, the dyslipidemia of PCOS correlates with hyperandrogenemia [13], and treatment of the latter leads to improvements in lipid profile[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]. Ideally, long-term treatments of PCOS should address not only endocrine dysfunction but also cardiovascular risks. Today various classes of drugs being used in PCOS women with various benefit. Recently, the use of statins emerged as a novel therapeutic approach to PCOS. In the first clinical trial, women with PCOS were randomized to treatment with simvastatin (20mg daily) plus oral contraceptive pill (OCP) or OCP alone [18]. After 12 weeks of treatment, women receiving simvastatin had significantly lower total testosterone and a better lipid profile than those taking OCP alone. Subsequent crossover of treatments and follow-up for 24 weeks has shown that simvastatin also improved chemical markers of systemic inflammation and endothelial function [19]. More recently, in a randomized, placebo-controlled trial, another statin, atorvastatin induced a significant decrease of testosterone, C-reactive protein, and insulin resistance, as well as improvement of lipid profile [20].

### Aim of study

The present study was designed to directly compare effects of metformin and atorvastatin on clinical and biochemical hyperandrogenism in women with PCOS as well as to determine whether a combination of these treatments is superior to either monotherapy.

### Subjects and methods

### Subjects

This randomized, open labeled clinical study was conducted at Al- Basra Hospital for Maternity and children while patients attending the outpatient clinic of Gynecology from October 2011 till the end of December 2012. One hundred and eight women with PCOS were enrolled in this study, age (28.31 ± 0.51) and body mass index (BMI) (26.64 ± 0.28), in addition we recruited forty five healthy women matched for age and BMI as control. All participants were gave informed consent, and the study was approved by the committee ethics of Baghdad University College of Pharmacy and by AL-Basra Health Directorate. The diagnosis of PCOS was made 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[21, 22] depending on ultrasound examination, clinical features and laboratory hormonal tests by specialist gynecologist. The inclusion and exclusion criteria of women enrolled in this study are shown in table

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(2.1). Exclusion was made depending on question and clinical features or laboratory tests. Subjects were advised not to change their lifestyle, including physical activity or dietary habits, during the study period.

**Study design**

Eligible PCOS patients were divided randomly into three groups: group I (n=34, treated with metformin 850mg twice daily), group II (n = 38, treated with atorvastatin 20 mg once daily) and group III (n=36, treated with metformin plus atorvastatin with the same dose used in previously mentioned groups). Metformin (Glucophage)® was provided from Merck Serono company France while atorvastatin (Lipitor) ® was provided from Parke-Davis company USA. Parameters evaluation and follow up were performed at baseline and after 3 months of treatment during the follicular phase of a natural menstrual cycle or after medroxyprogesterone-induced menses.

Evaluation included determinations of body mass index BMI (BMI was calculated as follows:

BMI = weight (kg)/height ($m^2$)), scoring of hirsutism using Ferriman and Gallwey score (score > 9) [23], and acne score. Acne was evaluated using a four-grade scale: (0: no acne; 1: minor acne, face only; 2: moderate acne, face only; 3: severe acne, face and back or chest[24]. After 12 hours fasting, venous blood samples, about 10 ml were collected from patients and healthy volunteers in aplastic plane tubes. After allowing the blood to clot at room temperature for 30 min, blood samples were centrifuged at 3000 rpm for 15 min. Fresh serum was used for assessing the serum levels of total and free testosterone, sex hormone binding globulin and androstenedione by Enzyme linked ImmunoSorbent Assay (ELISA) KITS[25, 26, 27, 28]. Dehydroepiandrosterone sulfate (DHEAS) assay by competitive immunoenzymatic colorimetric Kits[29]. The FAI was calculated as the (total testosterone X 100/SHBG). All values are expressed as mean ± standard error of the mean. Data were analyzed using Microsoft office Excel 2010 software for all mathematics and statistical analysis. The ***student's t test*** was used to determine the significant difference in means of groups. P< 0.05 was considered to be the lowest limit of significance.

**RESULTS**

Demographic presentation of all women enrolled in study is shown in table (3.1). As it is presented all groups were match in age and BMI, however there was significant elevation in hirsutism and acne score and high percent of menstrual irregularity in all treating group as compared to control group. Yet there was no significant difference in hirsutism and acne score and percent of menstrual irrgularity among treating groups. Table (3.2) show the clinical and biochemical parameters women enrolled in study. There was significant elevation in serum level of free and total testosterone, FAI, DHEAS, and androstenedione in women with PCOS as compared to healthy control women, however there was significant reduction in serum level of SHBG in women with PCOS as compared to control. Concerning women with PCOS those enrolled in present study, there was no significant difference in base line value of free and total testosterone, FAI, DHEAS, SHBG and androstenedione among different treating groups.

**Effect of treatment**

As shown by table (3.2) after 3 month of treatment with metformin 850 mg twice daily (group I), there was significant (p<0.05) reduction in serum level of testosterone (free and total), and in FAI as compared to their base line values. However there was significant elevation in serum level of SHBG in group I after 3 months treatment as compared to their base line values. Yet there was no significant effect of metformin after 3 months on serum levels of DHEAS, androstenedione or on hirsutism or acne score. On the other hand there was significant reduction in serum levels of testosterone (free and total), DHEAS, and significant elevation in serum level of SHBG in group II after 3 months treatment as compared to their base line and group I values. There was significant reduction in serum level of androstenedione in group II after 3 month as compared to their base line values. There was no significant changes in hirsutism or acne score in group II after 3 months of treatment. Treatment with metformin plus atorvastatin (group III) show significant improvement in all clinical and biochemical parameter (significant reduction in BMI, free and total testosterone, FAI, DHEAS, androstenedione, hirsutism and acne score and significant elevation in SHBG. However women in group III had significantly lower value of (BMI, free and total testosterone, FAI, DHEAS) and significantly greater level of SHBG after 3 months of treatment as compared to their values in group I and group II.

**DISCUSSION**

Hyperandrogenemia or clinical manifestations of hyperandrogenism, such as hirsutism, acne and male pattern balding, are common among women with PCOS. In fact, up to 90% of women with PCOS have increased androgen levels[12]. Hyperandrogenaemia represents an independent risk factor for development of hypertension and increased cardiovascular risk in women with PCOS [30 31]. In regarding to hirsutism, androgens are involved in the irreversible transformation of fine vellus hairs into coarse terminal hairs [32]. Androgens also involved in 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 [33]. Furthermore, Hyperandrogenism can lead to a decrease in insulin sensitivity and glucose intolerance, a risk factor for metabolic syndrome[34,35]. Thus hyperandrogenaemia is one of the main targets for treatment to improve quality of life and decrease morbidity in PCOS.

Our result showed that as compared with healthy women (matching age and BMI), women with PCOS had significant elevation in serum level of free and total testosterone, DHEAS, androstenedione, FAI, hirsutism sore and acne score and **(**table 3.1 and 3.2 ). While there was significant reduction in SHBG in PCOS women in either treating group as compared to healthy women. There was no significant difference in either base line parameter among treating group. This in agreement with several clinical studies that showed significant elevation of androgen level in women with PCOS [36, 37], hirsutism presents in approximately 60% [38, 39] and acne in 15% [40]of women with PCOS. The Marked increment in serum total and free testosterone may be due to excess ovarian production of androgens, which is considered to be central in the diagnosis of PCOS [41]. However some researchers have shown apparently normal testosterone concentrations in their PCOS studied groups, which may be attributed to their low to normal sex hormone binding globulin levels [42].

As shown by table (3.2) after 3 month of treatment with metformin 850 mg twice daily (group I), there was significant (p<0.05) reduction in serum level of testosterone (free and total), in FAI and significant increment in serum level of SHBG, however there was no significant effect of metformin on serum levels of DHEAS, androstenedione or on hirsutism or acne score. This is in consistence with other clinical studies that shown testosterone level was improved in women with PCOS after metformin treatment[43, 44]. Administration of metformin has beneficial role in reduction serum testosterone level by exerting its action as insulin sensitizing agent[45]. Metformin improve insulin sensitivity and attenuate insulin resistance in women with PCOS, furthermore metformin may has a direct inhibitory effect on the expression of various enzymes involve in thecal cell steroidogenesis and androgen production[46]. Yet other study shown no significant reduction of serum androgen after treatment with metformin, Nazli N. study 2011 demonstrated that after three months treatment with 500mg three times daily of metformin in 200 women with PCOS, there was no significant improvement in clinical and biochemical hyperandrogenism[47].

This discrepancy in the studies regarding metformin created an interest for evaluating any beneficial effects of statin (atorvastatin in present study), alone or in combination with metformin, on the hyperandrogenemia or clinical manifestations of hyperandrogenism outcomes in women with PCOS. Atorvastatin like other statin exert its action by competitive inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway[48]. 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 [49].

Present results showed that after three months of treatment with 20 mg daily of atorvastatin (group II), there was a better improvement in biochemical hyperandrogenism as indicated by significant reduction in all measured hormones and FAI and significant elevation in SHBG. This in agreement with **Sathyapalan 2009**[50] **who** shown after 12 weeks treatment with 20 mg atorvastatin there was significant reduction in FAI, testosterone together with significant increase in SHBG in 40 women with PCOS and with **Kaya 2009 study**[51] who showed that after 12 weeks of treatment with either simvastatin or atorvastatin there was significant reduction in serum level of free and total testosterone in 52 women with PCOS.

**Table (2.1):** Inclusion and exclusion criteria of women enrolled in Study.

| Inclusion criteria | Exclusion criteria |
|---|---|
| -Single women newly diagnosed with PCOS according to modified Rotterdam criteria.<br>-Age (18-39year)<br>-BMI 18-30 Kg/$m^2$<br>- Normal hepatic and renal function<br>- No history of cardiovascular diseases. | - Women who had diabetes mellitus, hyperprolactinemia, congenital adrenal hyperplasia, thyroid disorders, Cushing syndrome, androgen secreting tumors, hypertension, smoking.<br>- women they had been treated with any hormone and confounding medications, including oral contraceptive agents, antilipidemic drugs, and insulin-sensitizing drugs that might affect the ovarian function and/or metabolic criteria, within 3 months before enrollment. |

**Table (3.1):** Demographic presentation of 108 women with PCOS and 45 healthy controls women.

| Characteristics | Control (N=45) | Group I (N= 34) | Group II (N= 38) | Group III (N= 36) |
|---|---|---|---|---|
| **Age** | 27.58±0.84 | 29.03±0.93 | 28.66±0.81 | 27.25±0.89 |
| **BMI (Kg/m)** | 26.05±0.43 | 26.09±0.59 | 27.07±0.4 | 26.73±0.49 |
| **Menstrual irregularity** | 4 (8.9%) | 28 (82.4%) | 31 (81.6%) | 29(80.6%) |
| **Hirsutism score** | 4.12±0.27 **abc** | 9.27±0.41 | 8.84±0.37 | 9.49±0.37 |
| **Acne score** | 0.42±0.03 **abc** | 1.3±0.7 | 1.22±0.02 | 1.45±0.03 |

BMI: body mass index. P< 0.05 was considered to be the lowest limit of significance. **a** significant at p< 0.05 as compared with metformin values ; **b** significant at p< 0.05 as compared with atorvastatin values ; **c** significant at p< 0.05 as compared with atorvastatin plus metformin values**.**

**Table (3.2):** Pre- and post-interventional variables in healthy and women with PCOS.

| Variables | Base line | after 3 months | base line | after 3 months | base line | after 3 months | base line | after 3 months |
|---|---|---|---|---|---|---|---|---|
| | Control N= 45 | | Group I N = 34 | | Group II N= 38 | | Group III N = 36 | |
| Serum totat T (ng/ml) | 0.62±0.023 abc | 0.68±0.044 abc | 1.18±0.036 | 0.89±0.032* | 1.21±0.025 | 0.85±0.025* a | 1.15±0.033 | 0.76±0.024 *ab |
| Serum free T (pg/ml) | 1.22±0.07 abc | 1.19±0.07 ab | 3.44±0.15 | 1.64±0.05 * | 3.46±0.14 | 1.47±0.08*a | 3.62±0.19 | 1.11±0.1 * ab |
| SHBG (nmol/l) | 69.4±3.41 abc | 66.6±3.6 abc | 31.9±1.86 | 38.3±1.62 * | 31.6±1.67 | 48.4±1.81 * a | 29.9±1.9 | 56.5±2.02 * ab |
| FAI | 3.91±0.29 abc | 4±0.29 abc | 14.23±0.75 | 7.71±0.39 * | 14.74±0.75 | 6.5±0.32 * a | 15.42±0.71 | 5±0.18 * ab |
| DHEAS (µg/ml) | 2.03±0.1 abc | 1.97±0.1 abc | 3.26±0.11 | 3.24±0.12 | 3.33±0.12 | 2.44±0.11 * a | 3.18±0.1 | 2.1±0.1 * ab |
| Hirsutism sore | 4.12±0.27 abc | 4.3±0.25 abc | 9.27±0.41 | 8.79±0.55 | 8.84±0.37 | 8.33±0.41 | 9.49±0.37 | 8.06±0.37 * |
| Acne score | 0.42±0.03 abc | 0.39±0.29 | 1.3±0.7 | 1.26±0.07 | 1.22±0.02 | 1.08±0.03 | 1.45±0.03 | 0.96±0.03 * |
| Androstenedione (ng/ml) | 2.3±0.15 abc | 2.25±0.16 abc | 4.04±0.32 | 3.54±0.29 | 3.78±0.24 | 3.13±0.22 * | 3.57±0.23 | 2.89±0.2 * |

BMI: body mass index, T: testosterone, SHBG: sex hormone binding globulin, FAI: free androgen index, DHEAS: Dehydroepiandrosterone sulfate. All values are expressed as mean ± standard error of the mean. P< 0.05 was considered to be the lowest limit of significance. *significant at p< 0.05 as compared with base line values; a significant at p< 0.05 as compared with metformin values ; b significant at p< 0.05 as compared with atorvastatin values ; c significant at p< 0.05 as compared with atorvastatin plus metformin values.

In fact there are multiple pathways for statin to affect ovarian function in women with PCOS these include: Firstly, by directly inhibiting synthesis of cholesterol, which serve as substrate for testosterone synthesis, statins can also decrease the expression of different key enzymes which involved in testosterone production including P450scc, P450c17, and 3βHSD as demonstrated in ovarian cells[52] and in adrenocortical cells [53]. Secondly, statins can limit the actions of insulin and IGF-I on the ovary by both decreasing N-linked glycosylation and thus, maturation of insulin and Type I IGF-I receptors, and by decreasing isoprenylation of small GTPases, such as Ras and Rac, which mediate some pathways of insulin signaling (these GTPases modulate cells proliferation, apoptosis and function)[54]. By this, statins can attenuate the stimulatory effects of insulin on thecal proliferation and steroidogenesis. Thirdly, statins has direct and indirect antioxidant properties that can block the oxidative stress- mediated increases in cellular proliferation, steroidogenesis, and insulin resistance. The antioxidant actions of statins involve attenuation of nicotinamide adenine dinucleotide phosphate oxidize (NADPH) oxidize activity, preservation of relative levels of vitamins C and E, as well as inhibition of the uptake and generation of oxidized LDL[55,56]. Furthermore statins have intrinsic antioxidant activity including both anti-hydroxyl and anti-peroxyl radical activity [57]. Considering all above mechanisms gave raise the fact that use of statins in women with PCOS could decrease thecal hyperplasia, hyperandrogenism, and oxidative stress. Given combination of metformin plus atorvastatin considered superior to use each one alone as show from presented results, where there was significant improvement in all clinical and biochemical hyperandrogenism after 3 month of treatment in addition to significant reduction in BMI as compared to pretreatment state, moreover there was significant improvement in free and total testosterone, DHES, FAI, SHBG and BMI after three months of treatment with combination (metformin plus atorvastatin) as compared to treatment with each one alone. This occurred as it's expected from using two drugs with different mechanism of action. Where metformin will improve insulin sensitivity and attenuate hyperinsulinemia and their consequences on ovary and androgen production together with atorvastatin which act to decrease androgen and attenuate insulin stimulatory effect on ovary.

In conclusion the use of atorvastatin in women with PCOS will improve hyperandrogenism better than do metformin, using combination of metformin and atorvastatin will represent novel combination to improve clinical and biochemical hyperandrogenism in women with PCOS. Present study represents the first study that comparing the therapeutic effect of metformin and atorvastatin and their combination on clinical and biochemical hyperandrogenism in women with PCOS.

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