Rosuvastatin Add On Metformin In The Treatment Of Polycystic Ovarian Syndrome

Ali I. Al-Gareeb1, Bassim I. Mohammad2 Wafaa Salah Abd Al- Amieer3 Thabat J. Al-Mayahi3
1 Assist Prof in Clinical Pharmacology, College of Medicine, Al-Mustansiriya University,
2 Assistant Professor, College of Pharmacy,University of Al Qadisiyah,
3 Consultant Obstetrician & Gynecologist, Al-Kadhymia Teaching Hospital,
E-mails: dr.alialgareeb78@yahoo.com, jumabassim@yahoo.co.uk, dr.wafaa@ycom, dr.thabatjumah@yahoo.com.

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Abstract:

Background:-Polycystic ovary syndrome (PCOS) is common in women of reproductive age and it`s commonly associated with endocrinial and biochemical derangements. Moreover PCOS also associated with increase cardiovascular risks such as adverse lipid profile and endothelial dysfunction. Recently, statins have been shown to improve endocrine and metabolic aspects of PCOS.

Aim of the study:-The aim of this study was to evaluate effects of rosuvastatin as adjuvant therapy in treatment of polycystic ovarian syndrome.

Materials and methods:-The study was conducted at Al-Kadhemia Teaching Hospital, Department of Obstetrics and Gynecology from February 2014 to December 2015. In this study 96 women with PCOS randomly divided equally to two study groups; Group A (in which patients were allocated to receive metformin (500 mg three times a day) plus rosuvastatin (10 mg/day) and Group B (in which patients were allocated to receive metformin (500 mg three times a day) plus placebo for 12 weeks. Blood samples were obtained before and after treatment for determination of fasting blood sugar, follicle stimulating hormone, luteinizing hormone, Dehydroepiandrosterone sulfate, serum testosterone and total lipid profile.

Results:-At the end of study period, 89 patients complete the study (45 patients in Group A vs 44 patients in Group B). There were a significant decreases observed in both groups with respect to body mass index, fasting blood glucose, testosterones and...
luteinizing hormone whereas dehydroepiandrosterone sulfate, total cholesterol, low-density lipoprotein cholesterol and triglyceride declined significantly only in Group A.

Conclusions: Rosuvastatin as adjuvant therapy in patients with polycystic ovarian syndrome has many beneficial effects.

Keyword: polycystic ovarian syndrome, Rosuvastatin, metformin.

Introduction:
Polycystic ovary syndrome (PCOS) is represent one of the prevalent endocrine disorders in women of reproductive age. Several studies assessing different populations estimate its frequency at about 8% of reproductive age women (1-3). A part from important sequelae of PCOS such as menstrual disturbance, infertility, and excessive hair growth, patient with PCOS also presented with wide range of secondary consequences including abnormal lipid profile, hypertension, insulin resistance, hyperandrogenemia and eventually amplified risk of cardiovascular injury (4-6).

An effective treatment of PCOS would combine a decrease in cardiovascular risks and an enhancement in ovarian function (7, 8). The documented lines for the management of PCOS include lifestyle alterations comprising weight loss and the use of pharmacological agents such as insulin sensitizer agents, contraceptive pills, antiandrogens and ovulation induction agents. Though, their influence on the reduction of cardiovascular risk is generally uncertain (8, 9). There is emerging evidence that HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors (statins) are beneficial in patients with PCOS (8, 10-12). Theoretically, numerous features of PCOS might be improved by usage of statins. Increasing evidence supports the belief that statins not just improve serum lipid state, but also exert a wide range of other cardioprotective properties, including improvement of endothelial dysfunction, normalized vasomotion, improved bioavailability of nitric oxide, anti-inflammatory effects, decrease level of serum C-reactive protein, reduction of adhesion molecules, plaque stabilization, stimulation of endothelial progenitor cell recruitment, immunomodulation and inhibition of myocardial hypertrophy (13).

More over In vitro studies have revealed that statins could also reduce androgen production by ovary through inhibiting proliferation and androgen production of theca-interstitial cells (14).

The objectives of this study was to investigate whether the use of rosuvastatin in addition to metformin in treatment PCOS patients would improve the clinical and biochemical hyperandrogenism and reduce cardiovascular risks

Patients and methods
This is a prospective, single blind randomized clinical trial conducted at the Department of Obstetrics & Gynecology at Al-Kadhemia Teaching Hospital in cooperation with Department of Clinical Pharmacology, College of Medicine, Al-Mustansirya University, Baghdad-Iraq. The study protocol was approved by Local Scientific Committee of Al-Mustansirya College of Medicine.

Patients were considered to have polycystic ovary syndrome (PCOS) according to modified Rotterdam criteria (7), i.e. in the presence of both of the following:

- Clinical and/or biochemical signs of hyperandrogenism.
- At least one of the following: oligoovulation or anovulation and/or polycystic ovaries.

Other possible etiologies such as Cushing’s syndrome, congenital adrenal hyperplasia, or androgen secreting tumors were excluded. Moreover, none of the enrolled patients had hyperprolactinemia, thyroid disease, diabetes mellitus, liver disease or renal disease. The possible teratogenicity of statins was clarified to all enrolled patients and accordingly they were asked to use barrier methods of contraception during the study period and this was obeyed by all of them. All the patients instructed same diet and exercise plan and were recommended not to change
their dietary habits or physical activity during the progress of the study. Participants were allocated from patients with PCOS who attended the Obstetrics & Gynecology Outpatient Clinic at Al-Kadhemia Teaching Hospital from February 2014 to December 2015. No one of the patients allowed to participate in this study until a written consent form was obtained from them as well as inclusion and exclusion criteria were confirmed to them. So the 96 women who agreed to the study were randomly allocated to two groups; group (A) in which patients received metformin (500 mg three times a day) in combination with rosuvastatin (10 mg/day); and group (B) in which patients received metformin (500 mg three times a day) in combination with placebo (sugar) 300 mg/day.

Examination of patients were performed at base line and after 3 months of treatment in order to determinations of body mass index (BMI) in addition to scoring of hirsutism according to the Ferriman-Gallwey scale (15). Polycystic ovarian presence was identified via standard ultrasonographic criteria. Also blood samples were obtained after an overnight fast from each participant before the treatment and after 3 months of treatment on the first day of a spontaneous or medroxyprogesterone induced menses. Blood samples were used to determine serum follicular stimulating hormone (FSH), luteinizing hormone (LH), dihydroepiandrosterone (DHEAS), total testosterone, fasting blood sugar and total lipid profile.

**Statistical analysis**

All data were analyzed using the statistical package of social sciences (SPSS) version 18 for windows program on the computer. Data were expressed as mean ± standard error (SE). Patients’ characteristics of two groups were compared by independent samples t-test while patients’ characteristics recorded at different time intervals for each group were analyzed using paired samples t-test (within group). A two-tailed probability value (p value) less than or equal to 0.05 was considered as significant.

**Results:**

A total of 96 women were enrolled for the study; eighty nine of them completed the full 3 month study whereas 3 patients from the Group A and 4 patients from Group B were dropout from the study within first month because of unknown reason.

The mean age of patients were comparable in both groups (Group A 27.4 ± 7.5 vs. Group B 26.8 ± 7.3; P = 0.73). Moreover there were no significant differences in other baseline parameters between the two groups. The patients in both treatment groups tolerated the treatments well, and none of them experienced significant side effects.

Effects of 3 months of treatments are summarized in Table 1. There was a significant comparable decline in BMI and fasting blood sugar (FBS) in patients of the two study groups. Also testosterone (T) and luteinizing hormone (LH) levels were decreased significantly in both groups, with more significant reduction were noted in Group A. Moreover dihydroepiandrosterone (DHEAS) was decline significantly in Group A only whereas there were no significant changes in patients DHEAS in Group B. These changes in androgen statues were associated with a comparable improvement of reduction of hirsutism in both groups.

There was a significant absolute reduction in total cholesterol, LDL, and triglycerides in patients treated with metformin in combination with rosuvastatin. In addition to that there was also significant increase in HDL in patients in Group A while Group B patients showed no significant changes in lipid profile parameters.
Discussion:
The present study demonstrated clearly that use of rosuvastatin together with metformin in women with PCOS are much more effective than use of metformin alone in improvement of their clinical, hormonal and metabolic statuses.

It has been found in the present study that after 3 months of treatment with metformin alone or in combination with rosuvastatin, there were significant comparable reduction in BMI and FBS of both studied groups in comparison to their base line value and this reduction in both of the previous 2 parameters could be attributed to the effect of metformin therapy. This findings are in agreement with many different previous studies that showed significant reduction of BMI and FBS in metformin treated patients with PCOS (16, 17). This reduction in BMI and FBS is of important therapeutic potential especially in those patients with PCOS as those patients already suffering usually from increase in body weight and insulin resistance that result in increased fasting insulin level and this state of hyperinsulinemia suggested to participate in pathogenesis of PCO (18).

This study shown that rosuvastatin in combination with metformin is more
effective in reducing both of clinical and biochemical hyperandrogenemia i.e. hirsutism, T, DHEAS, LH, and reversing the LH: FSH ratio in patients with PCOS. It’s well-known that the endocrine status of women with PCOS is characterized mainly by increase plasma concentrations of T and a high LH level (3). Furthermore, ovaries of women with PCOS are characteristically enlarged, and discrete follicles contain a prominently increased number of layers of androgen making theca cells (3, 7)

The present study demonstrated that treatment of PCOS patients with metformin alone result in significant reduction in T and LH but this reduction were much more significant when rosuvastatin used in combination with metformin. Numerous earlier studies have point out the beneficial effect of metformin on biochemical and clinical features of PCOS (19, 20), although others do not (21). Metformin therapy may leads to an improvement of hyperandrogenism either directly by inhibition of androgen production in human ovarian thecal cells (22), or indirectly by reducing insulin resistance which result in decrease plasma insulin levels and as a result of that insulin stimulates androgen synthesis in the ovary will reduce and sex hormone binding globulin synthesis in the liver will increase (23)

It’s interesting to find in this study that combination therapy with rosuvastatin result in not only more reduction in T and LH but also in significant reduction of DHEA. Rosuvastatin supposed to employ its actions mainly by inhibition of 3-hydroxy-3-methylglutaryl- coenzyme A (HMG-CoA) reductase, a rate-limiting step of the cholesterol synthesis (13). So drop of testosterone production may be due to reduced availability of cholesterol, a substrate for steroid and sex hormone production. Moreover previous studies have indicated that statin treatment reduces ovarian androgen production by interfering with growth of theca interstitial cells along with reducing theca interstitial cell steroidogenesis (14)

An increase of cardiovascular risk factors is a common finding in PCOS, including dyslipidemia that is revealed in an elevated total cholesterol, triglycerides, and LDL and decreased levels of HDL (4, 5). The most characteristic lipid change in patients with PCOS is reduced levels of HDL (24). Previous studies displayed that patients with PCOS have higher levels of serum TG, LDL and considerably lower levels of HDL compared with the normal population (4, 11, 12, 25).

An expected outcome of this study was significant improvement of lipid profile in Group A manifested by reduction of TG, total cholesterol, LDL and increased HDL. These results are in accord with preceding studies regarding the LDL, HDL and cholesterol levels (26, 27) nevertheless, the interesting finding in the present study is the significant reduction in TG levels in patients treated with combination therapy of metformin and rosuvastatin. In previous studies TG levels were unchanged (26) or even increased (27) and this may be because of oral contraceptive pill usage in these studies. Consequently, a reduction of TG in the present study may point out a synergic effect between metformin and rosuvastatin when they used in combination in treatment of PCOS.

In conclusion, the present study demonstrates that the combination of metformin and rosuvastatin 10 mg daily could lead to a better improvement in clinical statues, biochemical hyperandrogenemia and lipid profile in patients with PCOS when given over 3 months period. So Statin treatment may therefore prove to be a potentially promising adjuvant therapy for women with PCOS.
References:


