Rosuvastatin Add On Metformin In The Treatment Of Polycystic Ovarian Syndrome

Ali I. Al-Gareeb[1] Bassim I. Mohammad[2] Wafaa Salah Abd Al- Amieer[3] Thabat J. Al-Mayahi[3]
[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.wafaasa@yahoo.com, dr.thabatjumah@yahoo.com.

(Received 9/ 9 /2013 , Accepted 1 / 10 / 2013)

الخلاصة:

خلفية: تعتبر متلازمة المبيض المتعدد الكيسات من الحالات الشائعه لدى النساء في سن الإنجاب وانها ترتبط عادة مع اضطرابات في الغدد الصماء .وعلاوة على ذلك فان متلازمة تكيس المبايض ترتبط أيضا مع زيادة مخاطر القلب والأوعية الدموية كزياده الدهون الضاره و خلل وظائف الخلايا البطانية للاوعيه الدمويه.

الهدف من هذه الدراسة: لتقييم آثار رسيوفاستاتين كعلاج مساعد في علاج متلازمة المبيض المتعدد الكيسات

المواد وطرائق البحث: أجريت الدراسة في مستشفى الكاظمية التعليمي، قسم أمراض النساء والتوليد من فبراير 2014 وحتى ديسمبر عام 2015 حيث شملت هذه الدراسة 96 امرأة مع متلازمة تكيس المبايض قسمت عشوائيا بالتساوي على مجموعتي الدراسة. المجموعة (أ) والتي تم تخصيص المرضى فيها لتلقي الميتفورمين (500 ملغ ثلاث مرات يوميا)، بالإضافة إلى رسيوفاستاتين (10 ملغ / يوم) والمجموعة (ب) والتي تم تخصيص المرضى فيها لتلقي الميتفورمين (500 ملغ ثلاث مرات يوميا)، بالإضافة إلى عقار وهمي لمدة 12 أسبوعا. وقد تم الحصول على عينات من الدم قبل وبعد العلاج لتحديد نسبه الجلوكوز الصومي، هرمون منشط للحوصلة، هرمون منشط للجسم الأصفر ، ديهيدرو إيبي أندروستيرون ،التستوستيرون ، ومجموع الدهون في الدم.

النتائج: -في نهاية فترة الدراسة لوحظ ان 89 مريضا إكملوا الدراسة (45 مريضا في المجموعة الأولى مقابل 44 مريضا في المجموعة الثانية). بينت نتائج الدراسه ان هناك انخفاض كبير في كلا المجموعتين فيما يتعلق بمؤشر كتلة الجسم، والجلوكوز الصومي،هرمون منشط للجسم الأصفر و التستيترون في الدم في حين ان ديهيدرو إيبي أندروستيرون ، كوليسترول الدم، البروتين الدهني المنخفض الكثافه والدهون الثلاثية قد انخفضت احصائيا بشكل كبير فقط في المجموعة الاولى.

الاستنتاجات: - يعتبر استخدام الرسيوفاستاتين كعلاج مساعد في المرضى الذين يعانون من متلازمة المبيض المتعدد الكيسات علاجا له العديد من الآثار المفيدة.

كلمات الدلاله:- تكيس متلازمة المبيض، رسيوفاستاتين، الميتفورمين

Abstract:

Background:-Polycystic ovary syndrome (PCOS) is common in women of reproductive age and it's commonly associated with endocrinal 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.

Table 1. Patients' parameters in both groups at the baseline and after 3 months of treatment.

Variable	Group A (Metformin plus rosuvastatin)			Group B (Metformin plus placebo)			*(Group A vs. Group B) P-value*	
	Baseline (n=48)	3 months (n=45)	*P*-value	Baseline (n=48)	3 months (n=44)	*P*-value	Baseline	3 months
BMI (kg/m2)	.21 ± 1.6382	26.11± 1.52	0.035	27.3 ± 0.71	25.92	0.048	0.22	0.11
Hirsutism (Ferryman score)	8.6±2.5	7.4±1.7	0.018	8.4±2.2	8.01±1.9	0.058	0.43	0.078
LH (mIU/mL)	9.22 ± 1.21	6.56 ± 1.10	0.011	9.61 ± 1.42	7.24± 1.21	0.059	0.624	0.089
FSH (mIU/mL)	6.54± 1.05	6.29± 0.99	0.092	6.49± 0.98	6.19± 0.95	0.075	0.907	0.859
DHEA(µg /dL)	285±95	267±81	0.043	280±82	278±86	0.181	0.338	0.058
Testosterone (ng/mL)	0.81±0.09	0.62±0.11	0.032	0.82±0.08	0.76±0.09	0.052	0.592	0.128
Fasting glucose (mg/dl)	86.42±9.11	76±13.11	0.052	85.82±9.11	75±15.21	0.042	0.882	0.945
Total cholesterol (mg/dl)	209.43±29.81	161.23±35.75	0.001	215±33.42	202±37.67	0.063	0.129	0.001
LDL cholesterol (mg/dl)	128.66±24.93	110.12±15.03	0.001	130.21±27.15	127.95±25.82	0.119	0.093	0.001
HDL cholesterol (mg/dl)	51.37±2.92	56.37±5.17	0.052	50.55±3.17	51.98±3.85	0.085	0.177	0.059
Triglycerides (mg/dl)	104.75±33.54	77.86±40.14	0.001	107.43±30.64	101.67±28.63	0.122	0.259	0.001

Each value represents mean ±SD.

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:

1) Thornton EC, Von Wald T, Hansen K. Polycystic Ovarian Syndrome: A Primer. Medical Hypotheses. S D Med. 2015 Jun; 68(6):257-61.
2) Kamalanathan S, Sahoo JP, Sathyapalan T. Pregnancy in polycystic ovary syndrome. Human Reproduction. Indian J Endocrinol Metab. 2013 Jan;17(1):37-43.
3) Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nat Rev Endocrinol. 2011 Apr; 7(4):219-31.
4) Ebrahimi-Mamaghani M, Saghafi-Asl M, Pirouzpanah S, Aliasgharzadeh A, Aliashrafi S, Rezayi N, Mehrzad-Sadaghiani M. Association of insulin resistance with lipid profile, metabolic syndrome, and hormonal aberrations in overweight or obese women with polycystic ovary syndrome. J Health Popul Nutr. 2015 Mar; 33(1):157-67.
5) Ramanand SJ, Ghongane BB, Ramanand JB, Patwardhan MH, Ghanghas RR, Jain SS. Clinical characteristics of polycystic ovary syndrome in Indian women. Indian J Endocrinol Metab. 2013 Jan; 17(1):138-45.
6) Paterakis TS, Diamanti-Kandarakis E. Aspects of Cardiometabolic Risk in Women with Polycystic Ovary Syndrome Curr Obes Rep. 2014 Dec;3(4):377-86.
7) Kubota T. Update in polycystic ovary syndrome: new criteria of diagnosis and treatment in Japan. Reprod Med Biol. 2013 Jul;12(3):71-77.
8) Mahalingaiah S, Diamanti-Kandarakis E. Targets to treat metabolic syndrome in polycystic ovary syndrome. Expert Opin Ther Targets. 2015 Nov;19(11):1561-74.
9) Luque-Ramírez M, Alvarez-Blasco F, Botella-Carretero JI, Martínez-Bermejo E, Lasunción MA, Escobar-Morreale HF. Comparison of ethinyl-estradiol plus cyproterone acetate versus metformin effects on classic metabolic cardiovascular risk factors in women with the polycystic ovary syndrome. J Clin Endocrinol Metab. 2007 Jul; 92(7):2453-61.
10) Duleba AJ, Banaszewska B, Spaczynski RZ, Pawelczyk L. Simvastatin improves biochemical parameters inwomenwith polycystic ovary syndrome: results of a prospective, randomized trial. Fertil Steril. 2006 Apr; 85(4):996-1001.
11) Banaszewska B, Pawelczyk L, Spaczynski RZ, Dziura J, Duleba AJ. Effects of simvastatin and oral contraceptive agent on polycystic ovary syndrome: prospective, randomized, crossover trial. J Clin Endocrinol Metab. 2007 Feb; 92(2):456-61.
12) Sathyapalan T, Kilpatrick ES, Coady AM, Atkin SL. The effect of atorvastatin in patients with polycystic ovary syndrome: a randomized double-blind placebo-controlled study. J Clin Endocrinol Metab. 2009 Jan; 94(1):103-8.
13) Kavalipati N, Shah J, Ramakrishan A, Vasnawala H. Pleiotropic effects of statins. Indian J Endocrinol Metab. 2015 Sep-Oct;19(5):554-62.
14) Ortega I, Cress AB, Wong DH, Villanueva JA, Sokalska A, Moeller BC, Stanley SD, Duleba AJ. Simvastatin Reduces Steroidogenesis by Inhibiting Cyp17a1 Gene Expression in Rat Ovarian Theca-Interstitial Cells. Biol Reprod. 2012 Jan 30; 86(1):1-9.
15) Yildiz BO, Bolour S, Woods K, Moore A, Azziz R. Visually scoring hirsutism. Human Reproduction Update. Hum Reprod Update. 2010 Jan-Feb; 16(1):51-64.
16) Ladson G, Dodson WC, Sweet SD, Archibong AE, Kunselman AR, Demers LM, Williams NI, Coney P, Legro RS. The Effects of Metformin with Lifestyle Therapy in Polycystic Ovary Syndrome: A Randomized Double Blind Study. Fertil Steril. 2011 Mar 1;95(3):1059-66.e1-7.
17) Navali N, Pourabolghasem S, Fouladi RF, Nikpour MA. Therapeutic effects of biguanide vs. statin in polycystic ovary syndrome: a randomized clinical trial. Pak J Biol Sci. 2011 Jun 1; 14(11):658-63.
18) Raissouni N, Kolesnikov A, Purushothaman R, Sinha S, Bhandari S, Bhangoo A, Malik S, Mathew R, Baillargeon JP, Hernandez MI, Rosenbaum M, Ten S, Geller D. Altered glucose disposition and insulin sensitivity in peri-pubertal first-degree relatives of women with polycystic ovary syndrome. Int J Pediatr Endocrinol. 2012 May 29;2012(1):14.
19) Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene induced ovulation in the polycystic ovary syndrome. N Engl J Med. 1998 Jun 25;338(26):1876-80.
20) Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, Zanolin E, Muggeo M. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized double-blind, placebo controlled 6 month trial, followed by open long-term clinical evaluation. J Clin Endocrinol Metab. 2000 Jan; 85(1):139-46.
21) Eisenhardt S1, Schwarzmann N, Henschel V, Germeyer A, von Wolff M, Hamann A, Strowitzki T. Early effects of metformin in women with polycystic ovary syndrome: a prospective randomized, double blind, placebo controlled trial. J Clin Endocrinol Metab. 2006 Mar;91(3):946-52.

22) Young JM, McNeilly AS. Inhibin removes the inhibitory effects of activin on steroid enzyme expression and androgen production by normal ovarian thecal cells. J Mol Endocrinol. 2012 Jan 25;48(1):49-60.
23) Nestler JE, Jakubowicz DJ. Decrease in ovarian cytochrome P450c17alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. N Engl J Med. 1996 Aug 29;335(9):617-23.
24) Legro RS. Polycystic ovary syndrome and cardiovascular disease: a premature association? Endocr Rev. 2003 Jun;24(3):302-12.
25) Scicchitano P, Dentamaro I, Carbonara R, Bulzis G, Dachille A, Caputo P, Riccardi R, Locorotondo M, Mandurino C, Matteo Ciccone M. Cardiovascular Risk in Women with PCOS. Int J Endocrinol Metab. Int J Endocrinol Metab. 2012 Fall;10(4):611-8.
26) Duleba AJ, Banaszewska B, Spaczynski RZ, Pawelczyk L. Simvastatin improve biochemical parameters in women with polycystic ovary syndrome: results of a prospective randomize trial. Fertil Steril. 2006 Apr;85(4):996-1001.
27) Banaszewska B, Pawelczyk L, Spaczynski RZ, Dziura J, Duleba AJ. Effects of simvastatin and oral contraceptive agent on polycystic ovary syndrome: prospective randomized cross over trial. J Clin Endocrinol Metab. 2007 Feb;92(2):456-61.