Effect of simvastatin and combined oral contraceptive pills in the treatment of polycystic ovary syndrome

Asmaa abdul Razak hassan al-sanjary

ABSTRACT

Objective: this study compare the effect of combination of simvastatin with combined oral contraceptive (COCP) versus COCP alone on PCOS women with hirsutism

simvastatin plus COCP , then COCP alone .group II use COCP alone then COCP with simvastatin . Each treated for 12 weeks and assessment done before and after each treatment period. All the patients are attending the medical consultation center of niniva collage of medicine.

Results: Patients in group I have 20.3% improvement in ferriman and Gallwey score (FGS) ,and 49.62 % decrease in testosterone (T) after treatment with simvastatin and COCP for 12 weeks compared with 16.9 % improvement in FGS and 21.84 % decline in T after COCP treatment. Patient in Group II develops 13.4% decrease in FGS and15.97 % reduction in T after treatment with COCP alone compared to 28.92% reduction in FGS and 20% decline in testosterone after treatment with simvastatin and COCP, with significant difference at P value less than 0.05 and 0.01.

In group I : Total cholesterol, LDL decreased by 14.8% ,12.14% in the combined treatment compared with 7.94 % ,2.76% in the COCP with significant difference at p value of 0.05 and 0.01.TG decreased by 10 % compared to 11% increase in the COCP alone treatment. HDL increased by 10.5 % in the combined treatment compared to the 5.92 % increase in the COCP group with significant difference at p value of 0.05 and 0.01.

In group II : there is no significant difference in the decrease in cholesterol ,LDL level between COCP and combined treatment, cholesterol tend to decrease by 12.58 % and 12.1% and LDL by 9.9 % and 8.4 %. Triglyceride tend to be decreased by simvastatin and COCP treatment by 14.3 %, and to increased by 0.02 % by COCP with statistical significant difference at P value less than 0.05 and 0.01 .HDL tend to be increased by 8.9% by simvastatin and COCP and 8.7 % increase by COCP with no statistical significant difference.

Conclusion: the use of simvastatin combined with COCP can exert a beneficial effects on both endocrine and metabolic aspects of PCOS . simvastatin can improve hyperandrogenisim and hirsutism more than COCP alone and it have beneficial effect on lipid profile unlike COCP.

Keywords : PCOS; hirsutism ; simvastatin ; COCP.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age(1,2,3) .it's prevalence is different in diverse population and about 5 - 10% of reproductive age women have some features of PCOS(1,2,3,4,5,6,7) . At the Rotterdam ESHRE/ASRM consensus work shop group,2004 a refined definition for PCOS diagnosis was agreed : namely the presence of two out of the following three criteria:

1.Oligo- and /or Anovulation;

2.Hyperandrogenisim (clinical and or biochemical);

3.Polycystic ovaries by ultrasound(6,8,9).

PCOS is a collection of heterogeneous signs and symptoms that are gathered

together in a spectrum of presentation from mild to severe form of the disorder (7) .Clinically , the onset is usually started at the puberty and the most common signs of PCOS are hirsutism (90%) , menstrual irregularities (90%), and infertility (75%)7 ,10.

Obesity is common in PCOS patient with increased abdominal girth10 .In about 60% to 70% of patients with PCOS insulin sensitivity is decreased leading to insulin hypersecretion (10,11). Studies have demonstrated that PCOS is associated with an increased risk of glucose intolerance and type 2 diabetes mellitus, independent of body mass index (BMI) . A growing body of evidence suggests an association between PCOS and hypertension and markers of subclinical atherosclerosis and vascular dysfunction12 .

Dyslipidaemia may be present in up to 60-90% of women with PCOS .The alterations in lipid profile are often associated increase of atherogenic lipoprotein which is correlated to insulin level rather than genetic inheritance13.

These lifelong metabolic dysfunctions in women with PCOS exaggerates CVD risk especially after menopause (4,14,15,16),thus early diagnosis of PCOS and close long term follow up and screening for diabetes and cardiovascular disease is warranted17 .

In PCOS patients there is a Low grade chronic inflammation reflected by increased C-reactive protein(4,18), and homocysteine concentration(19,20) which can predict those patients at risk of developing CHD and type 2 diabetes .

Patients with PCOS also at increased risk of developing endometrial ,breast and ovarian cancer directly or mediated by their reproductive and metabolic alteration6,21 . Typically PCOS patient is first identified during the early reproductive years with progressive hirsutism which may be a better marker of hyperandrogenisim21.

Combined oral contraceptive pills (COCP) are the most often used treatment modality for PCOS patients and for symptomatic treatment of hirsutism acting at different levels to decease androgen , by interfering with folliculogenesis of androgen, decrease adrenal production, tends to elevate SHBG decreasing free androgen, and act directly on the skin at the level of hair follicle22. Despite this COCP still have unresolved issues concerning effect on lipid metabolism (depend on the type of gestagens) and decrease insuline sensitivity and deteriorate glucose tolerance .

The dyslipidaemia pattern found in PCOS patient of having lower HDL level ,higher LDL/HDL ratios and higher TG ,this suggest the use of lipid lowering drugs in the treatment of PCOS

Simvastatin which is HMG-CoA reductase inhibitors with intrinsic antioxidant properties ,it has multiple actions independent of their classic effect on lipoprotein. Statin use improve insulin sensitivity in patients with metabolic syndrome23 ,and exerts a broad range of other cardioprotective effect ,including anti inflammatory properties and improved endothelial function 24,25.

Statin also acts to inhibit proliferation of human theca –interstitial cells26 , thus simvistatin may decrease hirsutisim and serum testosterone in women with PCOS more than COCP and because it has teratogenic effect on pregnancy (pregnancy category X) it should be combined with COCP to avoid pregnancy and to increase benefit 27 .

Statin are among the most extensively investigated and prescribed pharmaceutical agents in current clinical use28 ,and may be a novel drug for treatment of polycystic ovary syndrome since several aspects of the syndrome can be alleviated by the use of statin.

Subjects and methods

Subjects:

PCOS was defined according to the recent Rotterdams European Society for human reproduction and emberyology ASHERE/ASRM-sponsored PCOS consensus Work shop,that is the presence of at least two of the three criteria:1.oligo or anovulation.2.clinical and /or chemical signs of hyperandrogenism.3.polycystic ovaries by ultrasound. after exclusion of other causes such as congenital adrenal hyperplasia ,cushing syndrome or androgen secreting tumors[6,8,9].Also other conditions as thyroid disease ,hyperprolactinaemia and diabetes mellitus were excluded. The standard ultrasound criteria was used to diagnose polycystic ovaries[8].

The study conducted on 50 patients attend the consultant medical center /ninava collage of medicine between January 2011 - January 2012 , 50 PCOS patients are involved in this study ,after taking consent ,all have hirsutism as their main complain, Ferrimann and Gallway score was used to determine the severity of hirsutism, patient was diagnosed to have hirsutism if the score is more than 8[29],and hyperandrogenism is diagnosed if the patient have serum total testosterone more than (0.9 ng /ml).

These patients included in the study were not using any form of treatment for the last 3 months as oral contraceptive pills or other hormonal or medical treatment that likely to affect menstrual or ovarian function or lipid profile.

Methods:

A data of 50 patients with PCOS and hirsutism was involved in the study, after taking consent, they were randomly assigned in this randomized cross over prospective study into two groups : group I received 12 weeks – course of simvastatin 20 mg daily at evening (Zocor 20mg SIVISTATIN MDS) and microgynon (levonorgestrel 0.15mg and ethinylestradiol0.03 mg, Bayer) , followed by additional 12 weeks course of COCP alone. The mean age of patient in this group was 23.56 years .Group II received first 12 weeks course OCPs alone followed by cross over and additional 12 weeks course of simvastatin and COCP ,the mean age of patients in this group 23.16 years. The primary end point was total testosterone and effect on hirsutism and the secondary point was the effect on lipid profile .

Study design and assays

Baseline evaluation were performed during the follicular phase of natural menstrual cycle or after medroxyprogesterone induced cycle . Examination include determinations of BMI ,waist to hip ratio and scoring of hirsutism using ferriman –Gallwey score[29] .Blood sample was collected at cycle day 3 with 14 hours over night fast, in sodium-EDTA tube for total testosterone and lipid profile measurment and changes in the ferriman Gallwey score was determined at baseline and at the end of each coarse that at 12 and 24 weeks . During treatment with simvastatin patients are instructed to avoid intake

of grapefruit juice due to increased toxicity .Subjects were asked about possible side effect of simvastatin therapy and combined oral contraceptive pills, liver function test was checked at 12, and at 24 weeks.
Paired sample t- test was used to assess the differences in the testosterone, lipid profile and hirsutism score.

Result

Patients in group I : we have 20.3% improvement in ferriman and Gallwey score after treatment with simvastatin and COCP for 12 weeks compared with 16.9 % improvement after COCP treatment.
Patient in Group II develops 13.4% decrease in ferriman gallwey score after treatment with COCP alone and 28.92% decrease after treatment with simvastatin and COCP. The observed difference between the 2 lines of treatment in the two groups was significant at P value less than 0.05 and 0.01 with more benefit after the combined treatment.

Total testosterone was measured at the baseline and at 12 weeks and 24 weeks ,in group I there is 49.62 % decline in the combined treatment and 21.84 % in decrease in the COCP ,in group II there is 15.97 % reduction in total testosterone in the COCP compared to 20% decline in the simvastatin and COCP group with significant difference at p value less than 0.05 and 0.01.
In group I total cholesterol is decreased by 14.8% in the combined simvastatin and COCP treatment group compared with 7.94 % in the COCP with significant difference at p value of 0.05 and 0.01. LDL decreased by 12.14% in the combined treatment compared to 2.76% decrease in the COCP group with significant differences at p value 0.05 and 0.01.Triglyceride decreased by 10 % in the combined treatment group compared to 11% increase in the COCP treatment. HDL increased by 10.5 % in the combined simvastatin and COCP group compared to the 5.92 % increase in the COCP group with significant difference at p value of 0.05 and 0.01.
Patients in group II : there is no significant difference in cholesterol ,LDL level between both treatment and combined treatment tend to decrease cholesterol by 12.58 % and 12.1% and LDL by 9.9 % and 8.4 %. Triglyceride tend to be decreased by simvastatin and COCP treatment by 14.3 %, and to increased by 0.02 % by COCP with statistical significant difference at P value less than 0.05.HDL tend to be increased by 8.9% by simvastatin and COCP and 8.7 % increase by COCP with no statistical significant difference . (table 1)

All of the above effect were observed in the absence of significant changes to BMI or WHR.
None of the subject experienced significant side effects in the course of this trial ,non develop muscle damage and liver function tests remained normal throughout the study.
One patient was excluded from the study because of development of hypertention on starting the COCP.

In our study these women with PCOS have some form of dyslipidaemia in about 88%. The most common abnormality in lipid profile of these patients is lower high density lipoprotein (HDL) cholesterol in 68 %of patients ,26% of patients tend to have higher total cholesterol level ,and 4% of patients have abnormally higher level of triglyceride TG and 4% of

patients have abnormally high low density lipoprotein
(LDL) , as in diagram 1.

Menstrual abnormalities was present in our patients as oligomenorrhoea in 27/50 patients (54%) , and 7/50 of these patients (14%) presents with amenorrhoea.as in diagram 2
Diagram 2: menstrual pattern in the study sample

Discussion

Hyperandrogenism is the key endocrine abnormality of PCOS and serves as the essential diagnostic criterion of the syndrome with significant effect of androgens on the metabolism of lipids or insulin sensitivity[22]. Life- long exposure to an adverse cardiovascular risk profile including dyslipidaemia, dysglycaemia and hyperinsulinaemia and with moderate oxidative stress associated with PCOS may lead to endothelial dysfunction and premature atherosclerosis [11,15] ,and this effect can occurs without obesity and magnified more by obesity[14]and more in amenorrheic patient.

COCP are the most often used treatment modality of PCOS ,they are used for the symptomatic treatment of hirsutism by suppressing androgen production and improve menstrual dysfunction but it have many unresolved metabolic issues concerning insuline resistance and effect on lipid profile (depend on type of gestagen)[22].In general the addition of antiandrogen to COCP has not appears to increase overall treatment benefit ,and each of these agents have been shown to reduce hirsutism with equivalent efficacy, and should be used with effective contraception because of possible fetal toxicity. Insuline sensitizing agents have little effect on hirsutism[21] .

Statin have been tried in this study to observe the effect of simvastatin 20 mg on both hirsutism, testosterone level and lipid profile. Statin act to inhibit metabolic pathway of cholesterol synthesis , so it reduce the availability of cholesterol for androgen synthesis ,also statin inhibit DNA synthesis in human ovarian thecal interstitial cells as described in in-vitro studies[26].Statin also has intrinsic antioxidant properties reaching various types of tissues and inhibit proliferation of several types of cells including vascular smooth muscles[26].

FDA classify statin as pregnancy category X mainly due to lack of studies in human, while animal studies shows that statin can affect implantation and placental formation leads to abortion, and it can lead to severe CNS defect and limb deficiency[27]. For that in this study simvastatin has been used with COCP in cross over study both to inhibit possible pregnancy and to compare their effect with COCP (the most common treatment of PCOS).

In PCOS, The alteration of lipid profile represents the most common marker of increased cardiovascular risk. women with PCOS tend to have dyslipidaemia in form of elevation of total cholesterol level ,reduction in high density lipoprotein (HDL) cholesterol, and elevation in the level of triglyceride and low density lipoprotein ,and is generally characterized by increased triglyceride and decreased HDL[(11,13,17,21,)]. In our study the most common abnormality is decreased HDL While increased triglyceride is relatively uncommon probably because of the young age of patients in this

study whose main complaint is hirsutism , a study designed in italy give similar result [13],also Rogerio describe that early changes in young PCOS patients is decreased HDL [17] .
Statin tend to reverse all these abnormalities in dyslipidaemic patients and has been shown to have beneficial effect on lowering abnormal high and even normal lipid values in our study on PCOS patients, without any change on weight or body fat distribution . Patients in the study show reduction of total cholesterol ,LDL by combined simvastatin and COCP more than with COCP ,while TG is reduced with combined treatment but it increase by COCP alone. HDL was increased more in simvastatin with COCP than by COCP. all this difference in lipid profile is statistically significant.

In healthy women using the COCP, it is known that oestrogen can increase HDL, microgynon containing (ethinyl estradiol and levonorgestrel) didn't significantly affect LDL ,increase TG, and more important that this change remains within the reference range and unlikely to have any clinically significant effect on the risk of cardiovascular diseases, in PCOS patients little attention has been given to the effect of COCP on lipid profile[22].

It's apparent from the above that use of simvastatin combined with COCP can exert a beneficial effects on both endocrine and metabolic aspects of PCOS . simvastatin can improve hyperandrogenisim and accompanied by improvement of hirsutism more than COCP alone and it reduce total cholesterol ,LDL , TG and elevate HDL, even more than the reference range unlike the COCP.

It is known that women with PCOS cluster risk factors for premature morbidity and mortality at young and at old age, and simvastatin seems to affect and reverse these factors acting at different levels and through- out life . PCOS should be diagnosed early at adolescence (hirsutism, oligomenorrhea persisiting more than 2 years, and characteristics of PCO by US ,all are required for diagnosis) and patients can benefit from treatment with COCP as it can treat menstrual irregularities and hyperandrogenism and can elevate HDL early in life and if hirsutism is sever and is the primary complaint then we can add simvastatin. Later in life patients should be screened for other abnormalities in lipid profile every 3 years or so through- out life especially after 35 years were other lipid abnormalities are common ,for that simvastatin can be added if dyslipidaemia is present .
Metformine still be used in PCOS for treating menstrual problem, infertility, insulin resistance but has no role in treating hirsutism.

Although simvastatin appear promising for PCOS, further studies are required to asses for other effect such as infertility before deciding that simvastatin could be a noval drug for this hetergenoeus ,prevalent syndrome of obscure aetiology.

Recommendation

Diagnosis of PCOS should be made early in life so an opportunity for preventive health care can exist and may alleviate risks for future metabolic and cardiovascular disease.

Because abnormal lipid profile is common in PCOS which should be considered as a risk factor for

cardiovascular disease ,screening and monitoring every 3-5 years for abnormal lipid in women older than 35 years of age.

PCOS patients early in life should be treated with COCP for treatment of menstrual irregularities and mild hirsutism and simvastatin can be added for increasing benefit especially if hirsutism is sever or if there is abnormal lipid profile.

Simvastain therapy in PCOS is of benefit for treating hirsutism with the effect is more perceived by patients with abnormal lipid profile as it is observed from the study.

Further studies required to determine the duration of therapy ,in the treatment of hirsutism long periods for years is required ,with interval every 6 months treatment of simvistatin and COCP is required.

Because the risk of PCOS is sever patients with polycystic ovaries require close follow - up for clinical features of the disorder.

Simvastatin is indicated as an adjunct to diet for treatment of hypercholesterolaemia. Simvastatin is indicated in patients at high risk of CHD (coronary heart disease) (with or without hypercholesterolaemia) including patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease

Use of simvastatin concomitantly with itraconazole, ketoconazole, erythromycin, clarithromycin, should be avoided.

Grapefruit juice (more than 1 qt/day): increased drug blood level increase the risk of adverse reactions by decreasing drug metabolism.

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parameters	S+COCP	COCP	COCP	S+COCP
FGS	20.30%	16.90%	13.40%	28.92%
S.testosterone	40.62%	21.84%	15.97%	20.00%
Total cholesterol	14.80%	7.94%	12.58%*	12.10%*
LDL	12.14%	2.76%	9.90%*	8.40%*
TG	10.00%	11.00%+	14.30%	0.02%+
HDL	10.50%+	5.92%+	8.90%+*	8.70%+*

All are significant changes at P-value less than 0.05 and 0.01,
*:no significant change
+ % increase

Table 1:% reduction in the parameters assessed during treatment of the two groups with S+COCP and with COCP alone.

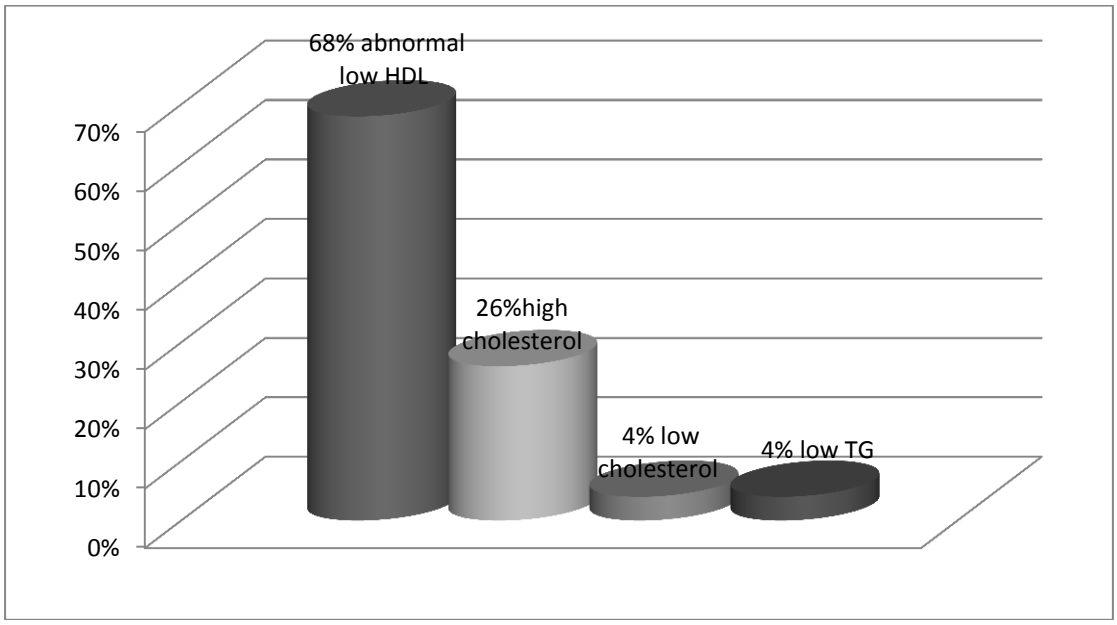
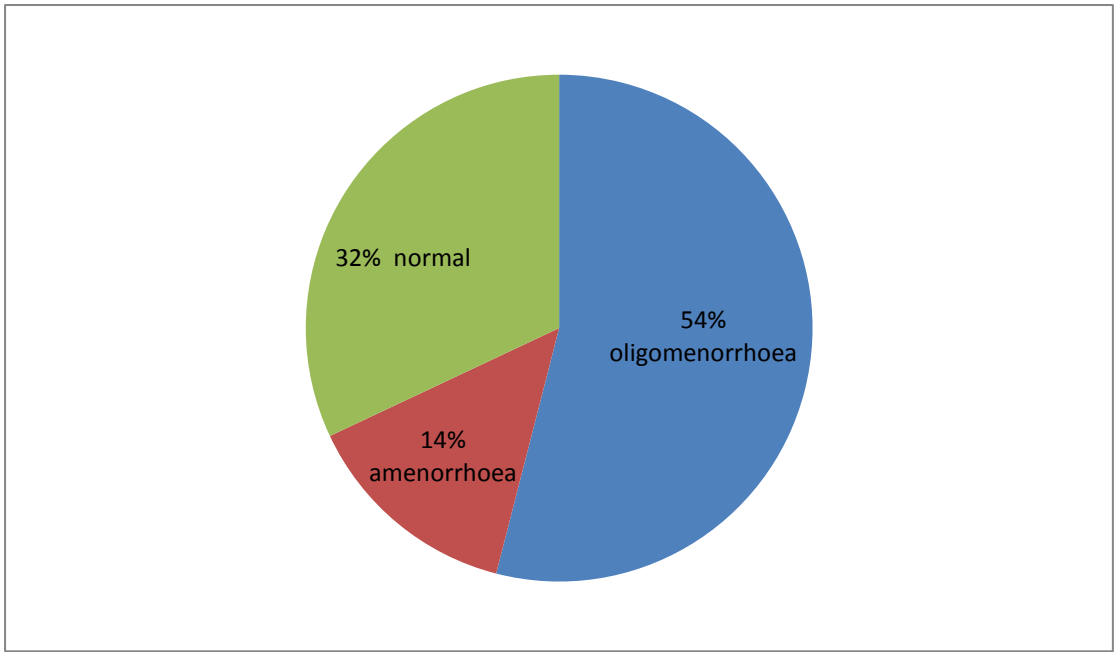


Diagram1:distribution of lipid abnormality in 50 patients with PCOS ,with primary complain is hirsutisim and mean age is 23 years.


32% normal
54% oligomenorrhoea
14% amenorrhoea