DOI: https://doi.org/10.53350/pjmhs22169295

ORIGINAL ARTICLE

Effect of Simvastatin on Polycystic Ovarian Syndrome (PCOS)

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ABSTRACT

Objective: To evaluate the effect of simvastatin on biochemical parameters in women with polycystic ovarian syndrome (PCOS).

Study Design: A prospective cohort study.

Place and Duration of the Study: The Department of Gynecology and Obstetrics, Ibn-e-Sina Hospital Multan, Pakistan from March 2021 to August 2021.

Material and Methods: The study was performed at the Department of Gynecology and Obstetrics, a tertiary care center affiliated with Ibn-e-Siena Hospital & Research Institute Multan, Pakistan. We screened 236 patients with PCOS ranging in age 20-40 years between March and August 2021.. Patients with hypothyroidism, congenital adrenal hyperplasia (CAH), Cushing syndrome (CS), ovarian tumors and on simvastatin therapy were excluded and those who were not willing to take part in this study were also excluded. All patients were given simvastatin 20 mg per day orally for 3 months. Venous blood samples were drawn before and after therapy and sent to the laboratory of the hospital for total cholesterol, total testosterone and low density lipoprotein (LDL-C) level. These tests were done before and after intervention with simvastatin treatment.

Results: Age range in this study was from 20 to 40 years with mean age of 29.41±4.44 years, mean duration of disease was 13.78±3.60 months, mean body mass index (BMI) 26.42±2.00 Kg/m^2 , mean Total Cholesterol 185.37±19.11 mg/dl, mean Total Testosterone 2.41±1.39 pmol/ L and mean LDL-C was 95.94±5.63 mg/dl. The majority of patients were from 20-30 years age group (68.6%). Decreased cholesterol was seen in 16.5% patients, decreased testosterone in 18.6% patients and decreased LDL-C in 28.8% patients.

Conclusion: The treatment of PCOS with simvastatin was found to be beneficial in improving several key features of PCOS including reduction in in total cholesterol, testosterone, and LDL-C levels.

Keywords: Polycystic ovarian syndrome, simvastatin, testosterone.

INTRODUCTION

The Polycystic ovarian syndrome (PCOS) is considered to be the most frequently seen endocrine abnormality among females of reproductive age, while its prevalence ranges between 5-21% among sexually active females.[1-4] The PCOS is estimated to affect about 75% of females suffering with infertility because of anovulation.[5] The main etiological factors behind PCOS are still not fully understood while genetic and environmental factors are thought to be behind the most common causes of PCOS. Most of the women with anovulatory infertility respond well to small amount of follicle stimulating hormone (FSH) along with clomiphene citrate therapy aiming induction of ovulation.[6,7] Some of the most common complications of PCOS are related to reproduction (hyperandrogenism, hissutism, anovulatory disorders, infertility and menstrual disorders), metabolism (obesity, diabetes and cardiovascular disorders) and psychological ailments (mood disturbances and low quality of life).[8,9]

The activity of statins targets several important pathophysiological features of PCOS, including its benefits on lipid profiling and cardiovascular risks. Researchers have also described statins to directly influence ovarian theca cell androgen synthesis, decrease in the cell proliferation and inducing apoptosis.[10] Research conducted on the effectiveness of simvastatin and atorvastatin seeking short-term outcomes has revealed beneficial effects of these drugs on the features of PCOS like reducing androgen levels, improving lipid profile and decrease in systemic inflammation.[11] A study found simvastatin treatment to result in reduction of total testosterone, total cholesterol and LDL cholesterol as 25.6%, 18.9% and 1.6% respectively among women with PCOS.[12]

As the data on this topic is very limited both at national as well as international level and to my best of knowledge there is no such published study in Pakistan but we treat patients with PCOS on a daily basis in our routine practice. Hence, conducting such study is need of the hour to document therapeutic outcomes of simvastatin in our population as there is no such study done in Pakistan. By this way, we might be able to offer our patients this treatment with more confidence if the results are found to be favorable in our population. This may help clinicians to treat these patients more efficiently without side effects, which will help to decrease disease morbidity in these patients. Objective of this study was to evaluate the effect of simvastatin on biochemical parameters in women with polycystic ovarian syndrome (PCOS).

MATERIAL AND METHODS

This prospective cohort study was performed at the Department of Gynecology and Obstetrics, a tertiary care center affiliated with Ibn-e-Siena Hospital & Research Institute Multan, Pakistan. -. Sample size was of 236 cases was calculated taking p = 18.9%[12] (decrease in total cholesterol) and d = 5% at 95% confidence level. Approval from Institutional Ethical Committee was sought. Informed consent was obtained from each patient after explaining the research and its objective. Patient were included only after they signed the informed consent.

A total of 236 women aged 20-40 years having PCOS with disease duration above 6 months were included. All women who were already taking simvastatin therapy or those having hypothyroidism, congenital adrenal hyperplasia, Cushing syndrome or ovarian tumors were excluded. Non probability, consecutive sampling was adopted. All the women as per inclusion/exclusion criteria of this study were registered from Department of Gynecology and Obstetrics, Ibn-e-Sina Hospital, Multan. All women were given simvastatin 20 mg per day orally for 3 months. Venous blood samples were drawn before and after therapy and sent to the laboratory of the hospital for total cholesterol, total testosterone and LDL-cholesterol (LDL-C) levels. Contact numbers of all women or their husbands were acquired for reminders of their follow-up visits. All the study data was noted on customized proforma.

Data was entered and analyzed in SPSS version 26.0. Mean and standard deviation (SD) were calculated for age, disease duration, total cholesterol, total testosterone, LDL - C and BMI.

Frequencies and percentages were shown for age groups, residential status, family history, family income and the number of women with decreases in total testosterone, total cholesterol and LDL-C. Effect modifiers like age, family history, residential status and BMI were controlled by stratification. Post-stratification Chi square test was applied, taking p-value ≤ 0.05 as significant

RESULTS

In a total of 236 women, the mean age was 29.4±4.4 years (ranging 20 to 40 years) while 162 (68.6%) women were aged between 20-30 years. The mean duration of the disease was calculated to be 13.8±3.6 months and the mean BMI was 26.42±2.00 Kg/m^2 while 140 (59.3%) women were overweight. Table-1 is showing baseline characteristics of all women studied.

Table-1: Socio-demographic characteristics of women with PCOS (n=236)

Characteristics		Number (%)
Age Groups (years)	20-30	162 (68.6%)
	31-40	74 (31.4%)
Area of Residence	Rural	107 (45.3%)
	Urban	129 (54.7%)
Duration of Disease (months)	≤12	83 (35.2%)
	>12	153 (64.8%)
Family History of PCOS	Yes	77 (32.6%)
Family Monthly Income (Pakistani Rupees)	≤ 25000	185 (78.4%)
	> 25000	51 (21.6%)
Body Mass Index	Normal	16 (6.8%)
	Overweight	140 (59.3%)
	Obese	80 (33.9%)

At baseline, mean total cholesterol was 185.4±19.1 mg/dl, mean total testosterone 2.4±1.4 pmol/L and mean LDL-C 95.9±5.6 mg/dl. After treatment of 3 months with simvastatin 20mg per day, a decrease in total cholesterol levels was seen in 39(16.5%) patients; a decrease in testosterone levels in 44 (18.6%) patients, and decrease in LDL-C in 68 (28.8%) patients, as shown in fig.1.

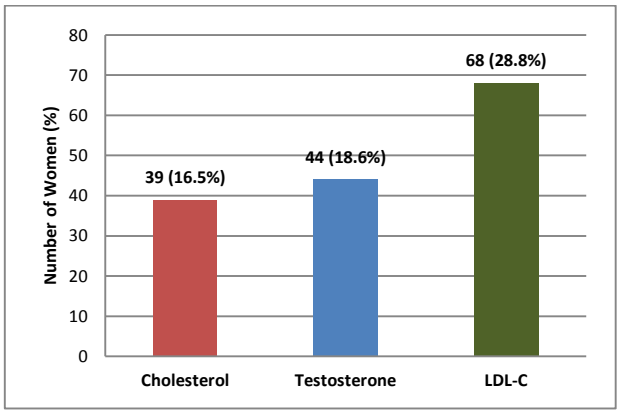

Figure-1: Percentage (%) decrease in cholesterol, testosterone, LDL-C Levels (n=236)

Stratification of baseline socio-demographic characteristics with respect to women with decreases in cholesterol, testosterone and LDL-C levels are shown in Table-2, 3 and 4.

Table-2: Stratification of baseline socio-demographic characteristics with respect to women with decrease in cholesterol levels after 3-months treatment with Simvastatin (n=236)

Characteristics		Decrease in Cholesterol		P-Value
		Yes (n=39)	No (n=197)	
Age	20-30	26 (66.7%)	136 (69.0%)	0.771
	31-40	13 (33.3%)	61 (31.0%)	
Residential Status	Rural	22 (56.4%)	85 (43.1%)	0.128
	Urban	17 (43.6%)	112 (56.9%)	
Duration of Disease (months)	7-12	14 (35.9%)	69 (35.0%)	0.917
	>12	25 (64.1%)	128 (65.0%)	
Family History of PCOS		12 (30.8%)	65 (33.0%)	0.786
Body Mass Index	Normal	5 (12.8%)	11 (5.6%)	0.033
	Overweight	27 (69.2%)	113 (57.4%)	
	Obese	7 (17.9%)	73 (37.1%)	

Table-3: Stratification of baseline socio-demographic characteristics with respect to women with decrease in cholesterol levels after 3-months treatment with Simvastatin (n=236)

Characteristics		Decrease in Cholesterol		P-Value
		Yes (n=44)	No (n=192)	
Age	20-30	30 (68.2%)	132 (68.8%)	0.942
	31-40	14 (31.8%)	60 (31.2%)	
Residential Status	Rural	18 (40.9%)	89 (46.4%)	0.513
	Urban	26 (59.1%)	103 (53.6%)	
Duration of Disease (months)	7-12	16 (36.4%)	67 (34.9%)	0.854
	>12	28 (63.6%)	125 (65.1%)	
Family History of PCOS		11 (25.0%)	66 (34.4%)	0.232
Body Mass Index	Normal	2 (4.5%)	14 (7.3%)	0.404
	Overweight	30 (68.2%)	110 (57.3%)	
	Obese	12 (27.3%)	68 (35.4%)	

Table-4: Stratification of baseline socio-demographic characteristics with respect to women with decrease in cholesterol levels after 3-months treatment with Simvastatin (n=236)

Characteristics		Decrease in Cholesterol		P-Value
		Yes (n=68)	No (n=168)	
Age	20-30	44 (64.7%)	118 (70.2%)	0.407
	31-40	24 (35.3%)	50 (29.8%)	
Residential Status	Rural	32 (47.1%)	75 (44.6%)	0.736
	Urban	36 (52.9%)	93 (55.4%)	
Duration of Disease (months)	7-12	27 (39.7%)	56 (33.3%)	0.353
	>12	41 (60.3%)	112 (66.7%)	
Family History of PCOS		26 (38.2%)	51 (30.4%)	0.242
Body Mass Index	Normal	6 (8.8%)	10 (6.0%)	0.535
	Overweight	42 (61.8%)	98 (58.3%)	
	Obese	20 (29.4%)	60 (35.7%)	

DISCUSSION

In this study, we demonstrated that simvastatin treatment resulted in improvement in features of. After treatment of 3 months with simvastatin 20mg per day, a decrease in total cholesterol levels was seen in 16.5% patients; decrease in testosterone levels18.6% patients and decrease in LDL-C in 28.8% patients. A study evaluating the effectiveness of simvastatin or metformin among women with PCOS found that significant improvement in reductions in total cholesterol and LDL-C levels were observed among women who were given simvastatin in comparison to women in the other group. In addition, it was observed that simvastatin alone resulted in significant reductions in hirsutism, acne, total and free testosterone.[12]

Inappropriate ovarian functioning may exhibit in the form of excessive androgen production, which is considered to be one of the major pathophysiological mechanisms behind PCOS. Ovaries of women affected with PCOS are usually enlarged while follicles may possess extra layers of androgen-producing theca cells.[13] Researchers in the past have established that theca cells in women affected with PCOS produce higher amount of androgens when compared to normal healthy females which might be resulting in terms of increased expressions of the key genes involved in androgen production, including the CYP11A gene encoding cholesterol side chain cleavage and the CYP17 gene encoding 17α-hydroxylase/17,20-desmolase.[14,15] Cassidy-Vu L et al[16] summarized 12 clinical trials evaluating the outcomes of statins among women with PCOS. It was noted that statins resulted in improvement in androgen levels and luteinizing hormone/follicle stimulating hormone ratio exhibiting improvement in cardiovascular risk factors.[16] In a recent meta-analysis conducted on randomized controlled trails seeking role of statins on hyperandrogenism in women with PCOS concluded that statins significantly reduce androgen levels and resulted in improvement in cutaneous manifestations of hyperandrogenism related to PCOS.[17]

In vitro trials have shown that statins resulted in reduction of cell proliferation, higher rates of apoptosis and demonstrated inhibition of testosterone production. In this study, these actions could have been responsible for the reduction in testosterone, total cholesterol and LDL-C levels.[14,18] Not much research has been done on evaluating effects of statins on the ovarian histology which might hypothetically show decline in ovarian volume along with reduction in the total number of theca cells.[19,20]

There are some limitations of this research. As we did not include any comparator group, randomized controlled trials comparing the effectiveness of simvastatin with placebo or other contemporary therapeutic options are available. We were also not able to measure to effect of possible life style and dietary modifications among women studied. As this was a single center study, our findings cannot be generalized. We only noted relatively short-term outcomes of simvastatin among women with PCOS, so further studies evaluating long-term outcomes need to be planned.

CONCLUSION

The treatment of PCOS with simvastatin was found to be beneficial in improving several key features of PCOS including reduction in total cholesterol, testosterone, and LDL-C levels. The findings of this study are highly encouraging in terms of short-term outcomes of simvastatin treatment among Pakistani women with PCOS. Further studies involving large sets of women with PCOS should be conducted comparing simvastatin with other contemporary therapeutic options aiming at improvement in features of PCOS.

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