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ROLE OF SIMVASTATIN IN ADDITION TO METFORMIN IN POLYCYSTIC OVARIAN SYNDROME PATIENTS, A RANDOMIZED CONTROLLED TRIAL ON PAKISTANI WOMEN

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Abstract:

Objective: *To study the effect of using simvastatin in addition to metformin in treatment of polycystic ovarian syndrome (PCOS) and its comparison with metformin alone therapy.*

Methods: *This is a randomized controlled trial conducted at Pakistan Institute of Medical Sciences (PIMS), during November 2014 to April 2015. Total 108 patients were enrolled in study and were stratified into two groups, consisting of 54 each. First group was given metformin alone while second group was given metformin and simvastatin. An extensive clinical history, menstrual history was taken from all participants and data was recorded on a pre-designed proforma. Complete clinical examination was performed on all patients. Abdominopelvic ultrasound was performed and volume >10cc or >12 follicles was labelled as enlarged. Lipid profile and LH/FSH ratio was performed at the time of enrollment and was repeated after 3 months to see response to treatment. The effective treatment response was more than 15% decrease in baseline values in comparison to data found at the time of enrollment.*

Results: *28.8±7.18 years was the mean age. The mean BMI was 22.5± 1.55 kg/m^2. The effective results were achieved in 66.7% patients in metformin alone group while in 92.6% patients in combination therapy group.*

Conclusion: *Simvastatin and metformin combination therapy is better than metformin alone for treatment of polycystic ovarian syndrome.*

Keywords: *Polycystic ovarian syndrome, females, metformin, simvastatin, lipid profile, LH/FSH ratio.*

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INTRODUCTION:

Polycystic ovarian syndrome is very common amongst reproductive age group females. It presents with menstrual irregularities usually oligo menorrhea or amenorrhea, obesity, hirsutism, infertility, insulin resistance. The baseline investigations are ultrasonography on which multiple follicles are seen in ovaries or ovarian size is enlarged. Other investigations are increased LH/ FSH ratio, raised serum lipids level [1,2,6].

Exact disease pathophysiology is not known yet. Hyper-androgenemia has been noticed in patients with PCOS along with insulin resistance and increased LH/FSH ratio [3,4]. Therapeutic approach for polycystic ovarian syndrome was studied by *Morgante G, et al* and was published in *journal of gynecological endocrinology in 2018*, in which exercise and life style modification has been given the leading importance for treating PCOS. Oral estrogen progesterone supplementations, anti-androgens play a vital role in reducing acne and hirsutism. For treatment of anovulation clomiphene citrate is the drug of choice. For weight reduction and insulin resistance, insulin sensitizers and statins are widely in practice and have shown beneficial effects [5].

Prof. Roger Hart, et al divided patients into 4 phenotype groups A, B, C and D based on serum androgens level, LH/FSH ratio and menstrual irregularities in his article about PCOS and its metabolic complications. The complications associated with PCOS are obesity, dyslipidemia, insulin resistance, cardio vascular disorders and thromboembolism [8]. Simvastatin is an HMG CoA reductase inhibitor. It has anti androgenic, antioxidant and anti-inflammatory properties which help reducing steroidogenesis of ovarian thecal interstitial cells. Due to above mentioned properties, use of simvastatin has been tested in many clinical trials in gynecology and obstetrics [1,2,3,7].

METHODOLOGY:

Total 108 patients were selected on basis of non-probability consecutive sampling technique. These were divided into two groups (n=54) each, first group was given metformin and second group was given metformin and simvastatin. Sample size was calculated by using WHO calculator with confidence interval of 95% and error of 5%. The study design was randomized control trial, conducted at PIMS, Islamabad, Pakistan from November 2014 to April 2015. No ethical issue certificate was collected from hospital ethical committee. 4.2% decrease in serum cholesterol level was expected by using metformin

alone and with simvastatin and metformin combination therapy 29.5% decrease in serum cholesterol was expected. Women of reproductive age group were enrolled in study (15 to 45 years) and were diagnosed cases of PCOS. Patients on OCPs, on any other hormonal medication, liver or kidney dysfunction, any other endocrine disorder were excluded.

Informed written consent was taken from all patients. Patients from both indoor and outdoor clinic were enrolled in study. Detailed clinical and menstrual history and clinical examination was performed. Ultrasound was performed at the time of enrollment. More than 10cc was considered enlarged for volume or more than 12 follicles was considered abnormal. LH/FSH ratio and fasting lipid profile was performed. LH, FSH levels were performed by electro chemiluminescence and lipid profile was performed by Hitachi 902. Patients were prescribed metformin 500 mg three times a day or metformin 500mg three times a day along with simvastatin 20mg once a day. Patients were followed up on outdoor basis for three months. Lost to follow up patients or those who were non complaint to prescribed drugs were excluded and new patients were enrolled. Investigations were repeated after 3 months and effective response to treatment was considered if there was more than 15% reduction in level of lipid profile and LH/FSH ratio.
Data was analysed using SPSS 11. Mean ± SD was calculated for age, parity, serum cholesterol, LH and FSH ratio and BMI. Foe drug efficacy, frequency and percentages were calculated. Chi square test was applied. P value less than 0.05 was considered statistically significant.

RESULTS:

Age group of patients was 28.8 ± 7.18 years. Mean BMI was 22.4 ± 1.5 kg /m^2. LH/FSH was 3.45 ± 1.8. Mean LH/FSH after three months was 2.3 ± 1.16. Mean baseline cholesterol was 242.8 ± 35.4 mg/dl. After three months cholesterol level dropped to 168.3 ± 16.2 mg/dl. Effective post trial results were achieved by 86 patients, 36 were from metformin only group and 50 were from simvastatin and metformin combination group. The p value was 0.001 which was statistically significant. Below 3 LH/FSH ratio was achieved by 41 patients, 16 were from first group and 25 from second group [table: 1]. There were 45 patients with LH/FSH ratio above 3, 20 patients were from first group while 25 were from

second. P value was 0.0082 which was statistically significant.

Efficacy in terms of serum cholesterol level (<220 mg/dl) was achieved by 36 patients, 29 patients were from first group while 7 were from second group. In 50 patients with serum cholesterol level >220 mg /dl, efficacy was achieved, 7 patients were from first group and 43 were from second group. Thus statistically significant difference was found between 2 groups. P value was 0.0004 which was statistically significant.

Stratification was done on basis of age, in age group less than 30 years, 21 (61.8%) showed effective response with metformin, while 26 (92.9%) with simvastatin and metformin. P value was less than 0.05. in more than 30 years old patients, 15 (75%) patients showed effective response with metformin alone and 25 (92.3%) patients showed effective response in combination drugs groups. P value was more than 0.05.

Table 1: Comparison between both groups on basis of LH/FSH ratio.

Efficacy	Metformin alone group	Metformin and simvastatin group	P value
LH/FSH ratio at treatment initiation			
<3			
Yes	16 (51.6%)	25 (86.2%)	0.082
No	15 (49.4%)	4 (13.8%)	
>3			
Yes	20 (87%)	25 (100%)	0.205
No	3 (13%)	0 (0%)	

Table 2: Stratification on basis of serum cholesterol level**.**

Efficacy	Metformin alone group	Simvastatin and metformin combination group	p-value
Serum cholesterol level <220 mg/dl			
Yes	29 (74.4%)	7 (87.5%)	0.77
No	10 (25.6%)	1 (12.5%)	
>220 mg/dl			
Yes	7 (46.7%)	43 (93.5%)	0.0004
No	8 (53.8%)	3 (6.5%)	

DISCUSSION:

Polycystic ovary syndrome is a common endocrinological dysfunction seen in females in reproductive age group. The presenting signs and symptoms of disease are infertility, insulin resistance, obesity, acne, hirsutism, thromboembolism. It is a common cause of mental stress amongst females due to infertility. *Navid B, et al* studied the attitude of PCOS patients towards the associated symptoms and complications and compared the PCOS patients with infertile women due to any other cause. It was concluded in the study that infertility was the major concern in PCOS patients, whether it was due to PCOS or any other cause. The social support and marital satisfaction amongst participants was also evaluated [9].

Therapeutic approach for polycystic ovarian syndrome was studied by *Morgante G, et al* and was published in *journal of gynecological endocrinology in 2018,* in which exercise and life style modification has been given the leading importance for treating PCOS. Oral estrogen progesterone supplementations, anti-androgens play a vital role in reducing acne and hirsutism. For treatment of anovulation clomiphene citrate is the drug of choice. For weight reduction and insulin resistance, insulin sensitizers and statins are widely in practice and have shown beneficial effects [5].

The complications associated with the current treatment approaches available for PCOS were studied by *Baldani DP, et al.* The PCOS patients are prone to suffer cardiovascular complications. The oral contraceptive pills used for the treatment of infertility and hirsutism amongst PCOS patients cause the cardiovascular damage [10]

Keeping in view the above mentioned discussion and complications associated with the treatment options available, the need to search for effectiveness of more drugs with fewer side effects in treatment of PCOS was felt. Simvastatin is an HMG CoA reductase inhibitor. It has anti androgenic, antioxidant and anti-inflammatory properties which help reducing steroidogenesis of ovarian thecal interstitial cells. Due to above mentioned properties, use of simvastatin has been tested in many clinical trials in gynecology and obstetrics [1,2,3,7]. Due to less research data available on Pakistani population, the authors aimed to conduct the clinical trial on the local population, so that disease burden can be reduced and lifestyle can be improved amongst PCOS patients.

CONCLUSION:

This is a randomized controlled trial conducted at Pakistan Institute of Medical Sciences (PIMS), during November 2014 to April 2015. Total 108 patients were enrolled in study and were stratified into two groups, consisting of 54 each. First group was given metformin alone while second group was given metformin and simvastatin. An extensive clinical history, menstrual history was taken from all participants and data was recorded on a pre-designed proforma. Complete clinical examination was performed on all patients. Abdominopelvic ultrasound was performed and volume >10cc or >12 follicles was labelled as enlarged. Lipid profile and LH/FSH ratio was performed at the time of enrollment and was repeated after 3 months to see response to treatment. The effective treatment response was more than 15% decrease in baseline values in comparison to data found at the time of enrollment. The result was 28.8±7.18 years was the mean age. The mean BMI was 22.5± 1.55 kg/m^2. The effective results were achieved in 66.7% patients in metformin alone group while in 92.6% patients in combination therapy group. It was concluded that Simvastatin and metformin combination therapy is better than metformin alone for treatment of polycystic ovarian syndrome.

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