

COMPARISON OF METFORMIN AND ORAL CONTRACEPTIVE PILLS IN THE TREATMENT OF POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

Objective: To compare metformin and oral contraceptive pills in terms of mean change of serum testosterone levels and body mass index in polycystic ovarian syndrome.

Study Design: Quasi experimental study.

Place and Duration of Study: Department of Gynecology and Obstetrics, Sargodha Medical College, Sargodha Pakistan, from Apr to Dec 2019.

Methodology: A total of 64 patients presenting with polycystic ovarian syndrome between 15-35 years were included. All patients were divided into two groups i.e. group 1 received oral contraceptive pills, and group 2 received metformin. Patients were clinically evaluated at baseline and 6 months after initial presentation to address the primary aim of evaluating the change in mean serum testosterone levels and body mass index after treatment.

Results: The mean age of patients was 20.30 ± 4.92 years. The mean body mass index of patients at presentation was 30.32 ± 2.66 kg/m². The mean reduction in the level of testosterone in group 1 was 5.14 ± 0.35 ng/ml while in group 2 it was 2.58 ± 0.41 ng/ml ($p < 0.001$) which was statistically significant. Mean decrease in body mass index in group 1 was 1.51 ± 0.71 kg/m² while in group 2 was 1.29 ± 0.46 kg/m² ($p = 0.148$) which was statistically insignificant.

Conclusion: Oral contraceptive pills were better than metformin in terms of mean decrease in serum testosterone levels in women presenting with polycystic ovarian syndrome while the mean reduction in body mass index in both the groups was similar.

Keywords: Body mass index, Metformin, Oral Contraceptives, Polycystic ovary syndrome, Testosterone.

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INTRODUCTION

First described in 1935, Polycystic ovarian syndrome (PCOS) is amongst the most common disorders of the endocrine system affecting women of the reproductive age group across the globe an approximate prevalence of 3.4-6.6% in the United States and 6.5-8% in European studies¹⁻⁴. A much higher prevalence of PCOS has been reported amongst the Pakistani women (52%) as compared to a prevalence of 20-25% in the women population of the United Kingdom⁵. It was the most common cause of hospital admissions for abnormal uterine bleeding in adolescent females⁶. Insulin resistance and obesity further aggravate the severity of the presentation⁷.

Management of PCOS is aimed at regularization of menstrual cycles along with ovarian testosterone suppression keeping in view the adverse effects profile of the various treatment options^{8,9}. One of the characteristic feature of PCOS is that approximately 50-70% of the patients suffer from variable spectrums of insulin resistance ranging from full blown diabetes mellitus

to insulin resistance. The hyperinsulinemia in patients with PCOS predisposes them to many cardiovascular and cerebrovascular diseases, metabolic syndrome, hypertension, and diabetes mellitus¹⁰.

Metformin is an insulin-sensitizing drug that has demonstrated promise in therapy for patients with PCOS while oral contraceptive pills (OCP's) have been the traditional go to option for patients with hyperandrogenism^{7,9}. The mechanism of action of metformin is mediated through increase in the insulin sensitivity, augmented secretion of estrogens, a reduction in the androgen levels and increased production of sex hormone binding globulin (SHBG)⁷.

OCPs cause a reduction in the circulating the levels of excess androgenic hormones by increase in the direct negative feedback signals on the LH secretion, and the net result is a decreased synthesis of androgens from the ovaries. Furthermore, they increase liver production of sex hormone binding globulin (SHBG) subsequently leading to increased binding of circulating free androgens and decreasing their levels⁹.

Keeping in view the magnitude of the problem and the limited number of studies available from Pakistan on this topic, this study was devised with the

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objective of this study was to compare metformin and OCPs in terms of mean change of serum testosterone levels and body mass index (BMI) in PCOS. The rationale of the study was to determine the better drug for lowering the testosterone levels in women with PCOS in our setup since the previous studies have had variable outcomes.

METHODOLOGY

A quasi experimental study was conducted on a total of 64 patients reporting to Government Mian Mola Buksh Hospital Sargodha and University medical and diagnostic center, Sargodha were enrolled in the study after taking permission from hospital ethical review committee (IRB certificate number: UOS/SMC/715/2019). Written informed consent was taken from all patients included in the study. The sample size calculated using WHO sample size calculator by taking level of significance as 5%; power of test=95%; population standard deviation=3.5¹¹; variance=12.25¹¹; test value of population mean=7.7¹¹, and anticipated population mean=4.8¹¹. The sample size came out to be 32 patients in each group, with a total sample size was 64 patients. The sampling technique was non-probability consecutive sampling.

The inclusion criteria included patients presenting with polycystic ovaries on vaginal ultrasound examination (≥8 sub capsular follicles, 3-8 mm in diameter involving one ovary along with increased stroma) and any one of the symptoms including clinical manifestations of hyperandrogenism, oligomenorrhea or amenorrhea, and/or an elevated serum testosterone level, at least 2 years post-menarche and age between 15-35 years. The exclusion criteria included patients with personal or family history of coagulopathies, pregnancy, severe migraines with aura, hypertension, breast cancer, and smoking.

Patients were divided into 2 groups; group 1 and group 2 containing 32 patients each by lottery method. The baseline serum testosterone levels and BMI were calculated for all patients. Group 1 patients received oral contraceptive pill {30µg ethinyl estradiol ± 0.15mg levonorgestril (once daily)} as a monthly regimen of 21 days followed by iron supplements for 7 days for 6 months. Group 2 patients received metformin at a dose of 1000mg twice daily for 6 months. Serum testosterone levels of the both groups was again determined after 6 months along with BMI. Data in both groups was recorded on a predesigned questionnaire.

Data was analyzed by using SPSS-23. For numerical variables including age, serum testosterone levels

and BMI, mean and standard deviation were calculated. Efficacy of drugs in terms of mean change in serum testosterone levels and mean reduction in BMI was compared between the two groups using independent sample t-test. The *p*-value ≤0.05 was taken as statistically significant.

RESULTS

A total of 64 patients were included in the study. The mean age of patients was 20.30 ± 4.93 years. The mean age of patients in group 1 was 19.74 ± 4.52 years and in group 2 was 20.86 ± 5.30 years. Majority of the patients (64.06%) were between 15-20 years of age. The mean BMI of patients was 30.32 ± 2.66 kg/m². The mean BMI at the time of presentation and after six months of treatment is shown in table-I.

The mean levels of testosterone at the time of presentation and after six months of treatment are shown in table-II. The mean reduction in the levels of testosterone and BMI after six months of treatment (table-III).

Table-I: Distribution of patients according to body mass index at presentation and after 6 months of treatment.

Body Mass Index (kg/m ²)	Group 1 (n=32)	Group 2 (n=32)	Total (n=64)
At Presentation	30.08 ± 2.76	30.55 ± 2.58	30.32 ± 2.66
After 6 months	28.57 ± 2.54	29.29 ± 2.52	28.93 ± 2.54

Table-II: Distribution of patients according to mean levels of testosterone (ng/ml).

Mean levels of testosterone (ng/ml)	At Presentation	After 6 Months	Reduction
Group 1 (n=32)	9.54 ± 0.29	4.40 ± 0.37	5.14 ± 0.35
Group 2 (n=32)	9.59 ± 0.37	6.98 ± 0.36	2.58 ± 0.41

Table-III: Mean decrease in levels of testosterone and body mass index in both groups.

Variable	Group 1	Group 2	<i>p</i> -value
Reduction in testosterone (ng/ml)	5.14 ± 0.35	2.57 ± 0.41	<0.001
Decrease in Body Mass Index (kg/m ²)	1.51 ± 0.71	1.29 ± 0.46	0.148

DISCUSSION

An estimated 50% of the patients with PCOS have their BMI in the obese range. While the levels of testosterone are a good predictor of the severity of the disease¹². The decrease in the BMI and levels of testosterone are thus important factors assessing the outcomes of patients undergoing treatment¹³⁻¹⁶. Our results showed a statistically significant mean reduction in the level of testosterone in OCP's group versus the metformin group (*p*<0.001). The mean decrease in BMI was

also more in the OCP's group but the difference was statistically non-significant ($p=0.148$). A Cochrane review by Tang *et al*, reported that metformin reduced the levels of testosterone and insulin in women suffering from PCOS¹⁷.

A study by Mhao *et al*, in 2015 found that treatment with metformin reduced the serum testosterone levels from 0.956 ± 0.31 to 0.486 ± 0.29 mg/dl which was statistically significant ($p=0.038$) as opposed to a decrease in testosterone levels from 1.177 ± 0.62 to 0.850 ± 0.3 mg/dl with OCPs which was statistically insignificant ($p=0.132$). The mean decrease in BMI was from 27.23 ± 5.44 to 26.12 ± 5.53 kg/m² in the metformin group ($p=0.000$) as opposed to a decrease from 30.50 ± 5.31 to 29.58 ± 5.02 ($p=0.048$) in the OCPs group¹⁸.

On the contrary, Al-Zubeidi *et al*, in 2015 compared the metformin and OCP's groups at baseline and then after treatment of 6 months and reported that a statistically not significant decrease in serum testosterone levels from 9.7 ± 3 to 7.7 ± 4 pg/ml with metformin ($p=0.15$) compared to a statistically significant decrease in serum testosterone levels from 9.1 to 4.8 ± 4 pg/ml with OCP's ($p=0.046$). The study also reported a mean decrease in BMI from 33.7 - 31.9 kg/m² in patients taking metformin ($p=0.004$) and a mean reduction in BMI from 33.4 to 32.9 kg/m², in those taking OCPs ($p=0.045$)¹¹.

In 2018, Kumar *et al*, reported that the mean BMI in the OCP's group decreased by 0.5 kg/m² which was statistically insignificant ($p=0.273$). The mean BMI in metformin group increased by 1.1 ± 0.1 kg/m² which was also statistically insignificant ($p=0.383$) which was comparable to our results. The mean reduction in levels of testosterone in the OCP's group was 0.16 ± 0.07 ng/ml which was statistically significant ($p<0.001$) whereas the mean reduction in levels of testosterone in the metformin group was from 0.04 ± 0.01 ng/ml which was statistically not significant ($p=0.224$)¹⁹. Suvarna *et al*, in 2016 reported that the two groups did not differ significantly in terms of decrease in serum testosterone levels ($p=0.65$)²⁰.

Despite the fact that OCPs were found to be a better treatment option, it is pertinent to mention that some patients' especially unmarried girls are reluctant to take OCPs when prescribed due to the social taboo attached in our population. However, better counseling of the patients as well as the parents can help with the treatment. The limitation of our study was the small sample size. We recommend further research

protocols with larger sample sizes to help devise evidence based research protocols from the data obtained from the local population.

CONCLUSION

OCPs were better than metformin in terms of mean decrease in serum testosterone levels while the decrease in BMI was found to be similar in both the groups in patients presenting with PCOS. The reduction in BMI was greater with OCP's than metformin although by a non-significant difference statistically. Therefore, we recommend the use of OCPs for the treatment of female patients presenting with PCOS.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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