

Efficacy of Metformin in Obese Versus non-Obese Women with Polycystic Ovary Syndrome (PCOS)

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ABSTRACT

Background: Polycystic Ovary Syndrome (PCOS) is a common cause of amenorrhea and infertility among women.

Objective: The study evaluated the efficacy of metformin in obese versus non-obese women with Polycystic Ovary Syndrome (PCOS).

Methods: A quasi-experimental study was conducted at a tertiary care center between March 2018 to December 2021. All patients who presented with chronic anovulation with oligomenorrhea or amenorrhea and polycystic ovaries on ultrasound were included in the study. Women with hyperprolactinemia, pregnancy, or lactation were excluded. Non-obese participants were labeled as "Group A" while obese were labeled as "Group B". Metformin therapy was initiated at an oral dose of 500 mg per day for the first week, followed by two times a day for another week. Ovulation and menstrual regularity were documented after six months of treatment. Metformin was considered effective if menstrual cycles were normalized and ovulation was achieved.

Results: The efficacy of metformin was 83.15% in non-obese women while in obese women it was only 53.65% ($p < 0.001$). The ovulation was more frequently achieved by non-obese women as compared to obese women [296 (83.15%) vs. 115 (32.3%); $p < 0.001$]. In lean patients fasting serum insulin reduced from 9.7 ± 3.4 mU/l vs. 6.2 ± 3.8 mU/l, ($p = 0.032$) while in obese patients, it changed from 20.2 ± 10.2 mU/l vs. 14.4 ± 3.2 mU/l ($p < 0.001$).

Conclusion: The study concluded that metformin was effective in improving symptoms of PCOS in patients irrespective of the body mass index.

Keywords: Polycystic ovary syndrome (PCOS), metformin, ovulation, obesity, amenorrhea, anovulation.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder among women of reproductive age with a prevalence of 5–10% [1]. The syndrome results in a wide range of issues, involving reproductive, metabolic, and cardiovascular systems resulting in long-term health disturbances that may impact the quality of life [2]. The characteristic features of PCOS include insulin resistance, an-ovulation, oligomenorrhea or amenorrhea and signs of androgen excess such as hirsutism and acne, in the absence of any other pathology that may cause similar symptoms [3]. Menstrual irregularities, an-ovulation and infertility are the common and distressing sequel of PCOS.

Drugs that increase insulin sensitivity, such as metformin, are of immense therapeutic importance either directly or

indirectly for the effective treatment of PCOS [4-6]. It is not certain whether patients suffering from PCOS in the absence of obesity and insulin resistance also benefit from insulin-sensitizing drugs. However, numerous studies have indicated that metformin does indeed have a positive impact and short-term trials on the effects of insulin-sensitizing drugs have shown promising roles in the improvement of insulin sensitivity, reduction of insulin secretion and regularization of menstrual cycles resulting in increased ovulation and fertility rates [2].

In a study on ovulation, Kumari AS and fellow researchers revealed that 88% of patients who were not obese and 29% of patients who were obese had ovulated following therapy, and the results were found to be statistically significant [6]. Another study by Tan S and co-workers showed that menstrual regularity was achieved in 59% of non-obese PCOS women as compared to 50% of obese females suffering from PCOS [7].

The findings of the current study will assess the comparative efficacy of metformin in correcting menstrual irregularity and ovulation in non-obese versus obese

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women with polycystic ovary syndrome. It will therefore help in better management of women with polycystic ovarian syndrome having different body mass indices.

MATERIALS AND METHODS

A quasi-experimental study was conducted at the Department of Obstetrics & Gynecology at Jinnah Postgraduate Medical Center and Dr. Ruth K. M. Pfau, Civil Hospital, Karachi, Pakistan between March 2018 and December 2021. The study was authorized by the ethical board prior to the data collection. A non-probability consecutive sampling technique was employed to recruit the participants in the study. For sample size calculation, the WHO sample size calculator was used. Using a reference study by Tan S *et al.* keeping the power as 90%, the confidence level was 95%, and the baseline BMI was $22.0 \pm 1.6 \text{ kg/m}^2$ versus $21.6 \pm 1.6 \text{ kg/m}^2$, after 6 months of metformin treatment, a sample size of 337 in each group was obtained [7].

Patients with elevated levels of testosterone as well as either oligomenorrhoea or amenorrhoea were diagnosed with PCOS as per the Rotterdam definition [8].

All patients with the diagnosed polycystic ovarian syndrome who presented with chronic anovulation with oligomenorrhoea or complete absence of menstruation, with clinically apparent features of increased androgen function along with the appearance of multiple ovarian cysts on ultrasound scan in at least one ovary, revealing a minimum of 12 follicles 2-9mm in diameter or a volume of more than 10 ml were included in the study. Women with peri-climacteric gonadotrophin values, hyperprolactinemia, hormonal treatment, pregnancy, or lactation were excluded.

Body Mass Index (BMI) was calculated by dividing the weight by the square height of the patient. The weight of the patient was determined using an electronic scale upon each follow-up and the height was measured with inch tape at presentation. Women with body mass index (BMI) of $> 29 \text{ kg/m}^2$ were considered obese while those with BMI between 25.0 and $<29 \text{ kg/m}^2$ were considered overweight as per WHO criteria while women who were between 18 and $< 25 \text{ kg/m}^2$ were considered as normal weight [9]. For this study, all individuals with BMI $< 25 \text{ kg/m}^2$ will be considered "non-obese or lean". Non-obese or lean participants were labelled as "Group A" while obese were labelled as "Group B." Hormonal assessment involved a second-day evaluation of the following hormones in the serum: Follicle stimulating hormone (FSH), luteinizing hormone (LH), Prolactin, testosterone, and mid-luteal phase progesterone.

Metformin therapy was initiated at an oral dose of 500 mg per day for the first week, followed by two times a day for another week and then was maintained at 1500 mg/day for six months in Group A. The dose was increased to 1000 mg twice a day in obese women. Follow-up was

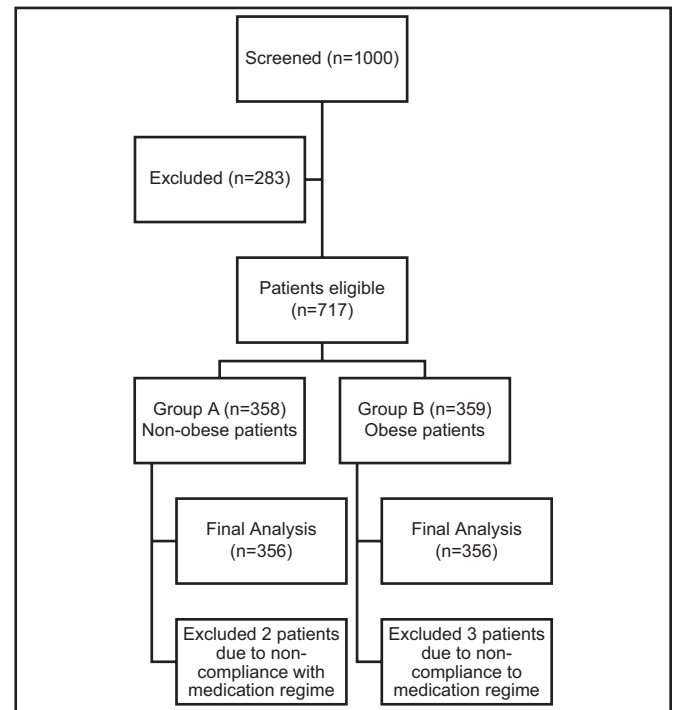


Fig. (1): Flow chart of patients in the study.

maintained every two weeks by the researchers by calling the patient on their phone number and requesting them to visit the outpatient department. Those experiencing any adverse effects or non-compliant patients were excluded from the final analysis (**Fig. 1**). Detailed clinical, biochemical and ultrasound examinations were repeated after 6 months. Ovulation and menstrual regularity were documented after six months of administration of metformin and all findings were noted on a predefined pro forma. Metformin was considered effective if menstrual cycles were normalized and/or if ovulation occurred. For the assessment of improvement in menstrual cycles, all patients were requested to record their bleeding periods in a calendar. Moreover, for ovulation determination, patients were asked to perform a home ovulation test at regular intervals or when they felt discomfort.

For all patients, biochemical analysis was done for determining the fasting blood glucose levels, testosterone levels, and insulin levels. Blood samples were drawn in an aseptic environment at baseline and follow-up periods (after six months of treatment).

Analysis of the data was done using the statistical package for social sciences (SPSS 25). Mean and standard deviation was found for quantifiable parameters including age and BMI. Shapiro-Wilk test was used to evaluate the normality of data. Frequencies and percentages were calculated for qualitative variables like menstrual regularity and ovulation. Paired t-test was applied to compare biochemical at baseline and sixth-month follow-up. A Chi-square test was used to compare the efficacy of metformin in both groups. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 712 patients were enrolled in the study with 356 in each group. The mean age of Group A patients was 28.23 ± 3.41 years while that of Group B patients was 27.45 ± 4.58 years. Table 1 shows the demographic and clinical characteristics of study participants. Most of the women were married. About 305 (42.8%) women had acne on presentation.

Table 1: Characteristics of Study Participants.

Characteristics	N (%)
Age (in years)	27.84 \pm 4.05
Age Groups	
20-25	97 (13.62)
26-30	297 (41.71)
31-35	192 (26.97)
35-40	126 (17.7)
Comorbidities	
Hypertension	200 (28.1)
Psychiatric illness	105 (14.7)
Ovulation	
Yes	411 (57.72)
No	301 (42.28)
Menstrual regularity	
Yes	423 (59.41)
No	299 (41.99)
Acne	
Present	305 (42.8)
Absent	407 (57.2)
Efficacy	
Yes	497 (69.8)
No	225 (31.6)

Table 2 illustrates the change in fasting blood levels, serum insulin, testosterone levels, and body mass index in lean patients at baseline *versus* six months after Metformin treatment. The study showed that with the exception of fasting blood sugar levels, all parameters significantly improved ($p < 0.001$).

Table 2: Biochemical analysis of lean patients with PCOS after metformin treatment.

Biochemical Parameters	Lean Patients (n=356)		p-Value
	Baseline	6-month Follow-up	
Fasting blood glucose levels (mg/dl)	85.2 \pm 4.6	83.2 \pm 6.4	0.145
Fasting serum insulin (mU/l)	9.7 \pm 3.4	6.2 \pm 3.8	0.032
Serum Testosterone (nmol/l)	7.8 \pm 3.2	2.4 \pm 1.2	<0.001
Body Mass Index (kg/m ²)	22.4 \pm 2.2	20.8 \pm 2.3	<0.001

Similarly, Table 3 demonstrated that significant improvements were observed in the fasting blood levels ($p < 0.001$), serum insulin ($p < 0.001$), testosterone levels ($p < 0.001$), and body mass index ($p < 0.001$) in obese patients at baseline *versus* six months after Metformin treatment.

The efficacy of metformin was 83.15% in non-obese women while in obese women it was only 53.65% which was significantly lower than the non-obese women

Table 3: Biochemical analysis of obese patients with PCOS after metformin treatment.

Biochemical Parameters	Group B (n=356)		p-Value
	Baseline	6-month Follow-up	
Fasting blood glucose levels (mg/dl)	105.1 \pm 48.0	88.1 \pm 12.1	<0.001
Fasting serum insulin (mU/l)	20.2 \pm 10.2	14.4 \pm 3.2	<0.001
Serum Testosterone (nmol/l)	2.8 \pm 3.4	2.2 \pm 1.8	<0.001
Body Mass Index (kg/m ²)	38.1 \pm 6.0	36.7 \pm 8.9	<0.001

($p < 0.001$). The ovulation was more frequently achieved by non-obese women as compared to obese women [296 (83.15%) vs. 115 (32.3%); $p < 0.001$]. A greater number of non-obese women had menstrual regularity after treatment with metformin as compared to obese women ($p = 0.019$) (Table 4).

Table 4: Factors affecting the efficacy of Metformin in patients with PCOS.

Characteristics	Group A (n=356) (n%)	Group B (n=356) (n%)	p-Value
Age (in years)			
20-25	45 (12.64)	52 (14.61)	<0.001
26-30	144 (40.45)	153 (42.98)	
31-35	101 (28.37)	91 (25.76)	
35-40	66 (18.54)	60 (16.85)	
Ovulation			
Yes	296 (83.15)	115 (32.3)	<0.001
No	60 (16.85)	241 (67.7)	
Menstrual regularity			
Yes	222 (62.36)	191 (53.65)	0.019
No	134 (37.64%)	165 (46.35)	
Efficacy			
Yes	296 (83.15)	191 (53.65)	<0.001
No	60 (16.85)	165 (46.35)	

Data is expressed as n(%)

DISCUSSION

Patients of PCOS exhibit features of either infrequent or complete absence of ovulation, along with clinically apparent signs of increased androgen secretions and multiple cysts in the ovaries. The intensity of symptoms is largely influenced by the patient's weight [9].

A disturbed balance between insulin sensitivity and b-cell activity has been described in both obese and non-obese women with PCOS. These women are at substantial risk of developing type 2 diabetes. The present study evaluated the efficacy of Metformin in obese *versus* non-obese patients with PCOS. Metformin is effective in normalizing the menstrual cycle and enhances the chances of ovulation. The effectiveness of Metformin has been best demonstrated in obese women and it was hypothesized that women with normal body mass index would not benefit from metformin however, the current study showed contrary findings. Our study showed that most of the non-obese women had ovulation and normal menstrual cycle after 6-months of treatment. A study by Stefano Palomba revealed

that administration of metformin (850 mg twice daily) for 6 months improved gonadotropin levels in patients with low levels of luteinizing hormone (LH) and Follicle-stimulating hormone (FSH), thereby promoting ovulation [10]. These findings were consistent with our current study, making the current trial more authentic.

Kumari AS *et al.* revealed that 88% of the non-obese and 29% of obese patients had successful ovulation post-treatment with metformin [6]. Another study by Tan S showed that menstrual regularity was achieved in 59% of non-obese PCOS women as compared to 50% of obese women with PCOS [7].

Multiple trials have shown that the effectiveness of metformin in the treatment of PCOS depends on parameters such as plasma levels of insulin and body mass index (BMI) [11]. A study found that metformin was 77.9% more effective in the stimulation of ovulation in non-obese women with PCOS, suggesting that metformin therapy is more effective in lean females suffering from the condition [12]. These findings were also supported in a study by Qadir *et al.* which noted that metformin was efficacious in 65.2% of cases of non-obese females with PCOS [13].

Some studies noted no difference between obese and non-obese patients, while other studies failed to evaluate insulin resistance in lean women suffering from PCOS [14-17]. Obesity worsens symptoms of PCOS, making weight loss essential in the management of PCOS, as it improves the frequency of ovulation, regulates the menstrual cycle, improves the endocrine profile and reduces the risk of a cardiovascular event [18, 19]. Metformin plays a role in weight loss by reducing satiety, but numerous trials have shown contrasting results regarding the effectiveness of metformin for weight loss in PCOS [20-22].

In the present study, we encountered certain limitations such as due to a large number of patients and limited resources, the follow-up data was extremely difficult to acquire. Oftentimes, patients were not compliant with their treatment regime and were therefore excluded. Moreover, since ovulation could not be determined for all patients clinically, and self-reported by patients using a home ovulation kit, it could have created bias. Nevertheless, this study is one of its kind because the data is extensive, and the study was multi-center.

We recommend that similar, multicentric studies with a diversified sample should be conducted to ascertain the findings of the current study for the better management of women with polycystic ovary syndrome having different body mass indices.

CONCLUSION

The current study concluded that metformin successfully improved symptoms of PCOS *i.e.*, reduced heavy menstrual bleeding, normalized menstrual cycles, and increased rate of ovulation among both lean and obese

women. Metformin was found to be associated with improved symptoms of PCOS in females irrespective of their body mass index.

ETHICS APPROVAL

Ethical approval was obtained from the IRB of JPMC with reference # NO F-2-81-IRB-/2019-GENL/32624. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration.

CONSENT OF PUBLICATION

Written informed consent was taken from the participants.

AVAILABILITY OF DATA

The authors confirm that data supporting the results of this study are available upon request to the corresponding author.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

All authors contributed significantly to the study.

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