Original Article

Efficacy and safety of metformin in over weight and obese patients with polycystic ovary syndrome

Ayesha Siddiqui[1], Moosa Khan[2], Tabassum Zehra[3], Syed Muhammad Masood Ali[4]

ABSTRACT

***Objective*:** To evaluate the efficacy and safety of metformin in overweight and obese women with polycystic ovary syndrome.

***Methodology*:** Forty-four overweight and obese female patients with diagnosed polycystic ovary syndrome were evaluated in an open label study. Patients were assigned metformin 500mg thrice daily for six months. The primary outcomes were to assess change in the fasting serum insulin level, fasting plasma glucose, insulin sensitivity, weight, BMI, Waist to hip ratio and ultrasonographic features of overweight and obese women. The secondary outcomes were systolic and diastolic blood pressure, menstrual cyclicity and hirsutism. The safety of intervention was assessed by recording the self-reported adverse effects and performing renal and hepatic profiles. The patients were evaluated at monthly intervals.

***Results*:** Forty subjects (90.9%) completed the study. At the end of six months, there was a significant effect of the drug on all the clinical parameters. Weight decreased from 85.71±1.04 to 84.38±1.02, BMI from 33.2±0.32 to 32.8±0.33($p < 0.05$) and Waist to hip ratio from 0.85±0.003 to 0.83±0.002.Ultrasonographic features, systolic and diastolic blood pressure also showed statistically significant improvement. Menstrual cyclicity, hirsutism, and metabolic parameters (serum fasting insulin level, fasting plasma glucose, HOMA index) also showed statistically significant improvement. The drug was well tolerated by the patients. No change was observed in blood urea, ALT and serum creatinine levels.

Conclusion: Metformin is a safe and effective drug for the treatment of obese and over weight, women with PCOS.

KEY WORDS: Polycystic Ovary Syndrome, Insulin resistance, Hirsutism, Ferriman-Gallwey Score, Obesity, Metformin, Body Mass Index, Waist Hip Ratio, Fasting Blood Sugar, Fasting Serum Insulin.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 5-10% women of reproductive age.[1] About 10% to 60% of women with polycystic ovary syndrome are obese. Central obesity with increased waist-hip ratio (WHR: 0.82-0.85) is a common finding among obese women with polycystic ovary syndrome.[2] The overall prevalence is reported to be 6% to 8% in general North American population, but the prevalence can be as high as 70% to 80% in women with oligomenorrhoea and 60% to 70% with

an-ovulatory infertility.[3] In a study conducted in Pakistan, the frequency of polycystic ovary syndrome was 17.6% with high rate of obesity (68.5%) and hyperinsulinemia (59%). Only 14% of women had normal BMI while 29.7% had BMI of 30 and 28.8% had a BMI above 30-35.[4]

Insulin resistance is a key contributor to the complexity of the pathophysiology of PCOS. Women with PCOS exhibit increased impaired glucose tolerance, diabetes mellitus, and metabolic syndrome. The longer the interval between menstrual bleeds, the greater the degree of insulin resistance.[5] It is thought that obesity exacerbates the underlying insulin resistance in patients with polycystic ovary syndrome.[6]

Metformin is a second-generation biguanide. It activates glucose transporters to facilitate passage of glucose into hepatic and muscle cells, thereby decreasing peripheral insulin resistance and lowering serum glucose levels but does not stimulate insulin release and, when administered alone, does not cause hypoglycemia.[7] In this study we assessed the efficacy of metformin in the treatment of PCOS.

METHODOLOGY

Study design: This was a prospective, open label study with convenient sampling, enrolling consecutive patients. The study was carried out in the Department of Pharmacology and Therapeutics, BMSI, in collaboration with the Department of Gynaecology and Obstetrics, JPMC, Karachi.

Study population: A total of 44 overweight and obese patients having polycystic ovary syndrome met the inclusion criteria and were enrolled after taking written informed consent. Out of total 44 patients, 6 were overweight and 38 were obese. The inclusion criteria were: female patients aged 18-42 years having infertility, oligomenorrhoea / amenorrhoea, obesity, hirsutism and ultrasonographic features of PCOS according to Rotterdam criteria.[8] Patients having medical problems such as hepatic or renal insufficiency, other endocrine disorders, morbid obesity >40kg/m^2, pregnant and lactating mothers and patients taking oral contraceptives were excluded from the study. Patients not compliant with medication or follow-up schedule were also excluded.

Study Protocol: This study enrolled patients from September to November 2009. All patients received metformin 500mg thrice daily and were followed up for six months. The patients were given the same advice concerning the benefits of lifestyle modification through diet and exercise. No additional advice or framework to assist weight reduction was given.

During this period monthly follow up visits were arranged and data recorded at each visit. The clinical parameters assessed at baseline and at monthly intervals following administration of metformin were: anthropometric measurement of height, weight, BMI, waist to hip ratio, menstrual cyclicity, and hirsutism as well as measurements of systolic and diastolic blood pressure and side effects and tolerability of the drug.

Overweight is defined as >25 kg/m^2 and obesity is defined as BMI>30 kg/m^2 according to W.H.O criteria of Obesity.[9] All patients were weighed wearing light clothes and without shoes on a platform scale with a 1.5 kg subtraction to correct clothing weight at each visit. Height was measured without shoes against a wall fixed tape BMI was calculated using the equation: weight (kilograms)/height (m^2). Waist and hip circumference was measured to the nearest centimeter with a soft tape according to W.H.O criteria. Waist circumference was obtained as the minimum value between the iliac crest and the lateral costal margin, whereas hip circumference was determined as the maximum value over the gluteal region. Menstrual cyclicity included oligomenorrhoea (fewer than eight cycles per year) or amenorrhoea fewer than two cycles per year. Hirsutism was evaluated by using Modified Ferriman-Gallwey score (FGS)[10], a score of >8 was indicative of hirsutism.

Systolic and diastolic blood pressure was measured with a mercury sphygmomanometer. The parameters assessed at baseline and at six months following administration of metformin were: fasting plasma glucose, serum fasting insulin and ultrasound assessments [all performed by the same observer] to assess ovarian morphology and follicular growth (numbers of follicles with diameter > 10 (2-10) mm in diameter, diameter of the largest follicle).[11] The participants were informed to contact the primary investigator in case of adverse events or pregnancy. The compliance was assessed by counting the empty sockets. Insulin sensitivity was evaluated by HOMA, calculated as fasting serum insulin (FSI) (µU/ml) x FBG (mg/dl)/405.

Statistical Analysis: Statistical software SPSS version 11.5 was used for data feeding and analysis. In the results number were given and percentages for qualitative/categorical variables (menstrual cyclicity and side effects). Mean and standard error of mean (SEM) was calculated for quantitative variables (age, weight, height, BMI, WHR, etc). Using Chi-square test for comparison of qualitative variables from day 0 to day 180 and student t-test was used for comparison of quantitative data from day 0 to day 180. A p-value of <0.05 was considered as statistically significant.

RESULTS

Forty-four overweight and obese patients were enrolled in the study but complete data of 180 days could not be obtained for four patients who failed to return for follow up and were excluded. Mean age±SEM of the patients was 24.4±0.26. The drug was well tolerated by the patients. Five patients (12.5%) developed nausea, four patients (10%) had transient vomiting and two patients (5%) had diarrhoea but the symptoms improved over a period of time as seen in Table-I.

Majority of the patients presented with oligo/amenorrhoea (92.5%), followed by infertility (90%). The mean weight (Kg) was 85.71±1.04 and height (cms) was 160±0.36 and mean BMI(Kg/m^2) was 33.2±0.32 at baseline and the weight decreased to 84.38±1.02 and mean BMI also decreased to 32.8±0.33($p < 0.05$). There was also a change in the pattern of distribution of body fat indirectly assessed by WHR, the mean WHR also decreased significantly from pretreatment 0.85±0.003 to post treatment 0.83 ± 0.002.The mean fasting blood sugar (mg/dl) decreased from 103.78 ± 0.51 to 92.20 ± 0.40 and mean serum fasting insulin level (mU/ml) pretreatment was 23.18 ± 0.38 to 10.13 ± 0.14 post treatment. The HOMA index also reduced significantly from 5.89 ± 0.12 to 2.28 ± 0.04.The ultrasonographic findings were seen in 26(65%), the number of follicles significantly decreased from baseline11.73±0.64 to 2.88 ±0.75 post treatment. The mean systolic blood pressure (mm of Hg) decreased from 130.50±1.18 to 121.50±0.37.The mean diastolic blood pressure (mm of Hg) also decreased from 83.00±0.73 to 80.88± 0.30. Weight, Waist hip ratio, FBS, FSI, Homa index and no. of follicles seen in ultrasound, systolic blood pressure and diastolic blood pressure were significantly decreased from day 0 to day 180 ($p<0.01$) as shown in Table-II. An overall improvement was seen in menstrual irregularity which was present in 37 women (92.5%) was observed in 4(10.0%) at the end of treatment ($p<0.05$) as shown in Fig 1.The mean hirsutism (FGS) was observed in 35 (87.5%) at baseline to 11 (27.5%) at the end of treatment. The mean FGS was 13.3±0.28 pretreatment to post treatment 9.5±0.15 ($p<0.05$) as shown in Fig 2. No significant difference was observed in the renal profile and hepatic profiles perfomed to assess the safety of Metformin from day 0 to day 180 ($p>0.05$) which included serum urea (mg/dl) at day 0 was 22.4±0.30 and at day 180, it was 22.40.41, serum creatinine (mg/dl) was 1.11±0.02 and 1.13±0.02 at day 0 and at day 180 respectively and serum ALT (U/L)

Table-I: Adverse effects observed in overweight and obese women with PCOS following metformin therapy.

Days	*Overweight & Obese women with PCOS* (n=40)		
	Nausea	*Vomiting*	*Diarrhoea*
Day – 0	-	-	-
Day – 30	5 (12.5%)	4 (10.0%)	2 (5.0%)
Day – 60	3 (7.5%)	2 (5.0%)	1 (2.5%)
Day – 90	1 (2.5%)	1 (2.5%)	2 (5.0%)
Day – 120	-	-	-
Day – 150	-	-	-
Day – 180	-	-	-

No significant difference from day 0 day 180 ($p>0.05$).

Table-II: Change in clinical parameters following metformin therapy in over weight and obese women with PCOS.

Clinical Parameters	*Overweight & obese women with PCOS (n=40)*	*P value*
	Mean±SEM	
Weight (kg)		
Day-0	85.71±1.04	<0.01
Day-120	85.28±1.02	
Day-150	85.05±1.03	
Day-180	84.38±1.02	
Waist Hip Ratio		
Day-0	0.85±0.003	<0.01
Day-120	0.84±0.003	
Day-150	0.84±0.002	
Day-180	0.83±0.002	
BMI(kg/m$^{2)}$		
Day 0	33.2± 0.32	<0.05
Day 180	32.8± 0.33	
Ultrasound – No. of follicles seen		
Day-0	11.73±0.63	<0.01
Day-180	2.88±0.75	
Systolic Blood Pressure(mm Hg)		
Day 0	130.50±1.18	
Day 180	121.50±0.37	
Diastolic blood pressure(mm Hg)		
Day 0	83.00±0.75	<0.01
Day 180	80.88±0.30	
Metabolic Parameters		
Fasting Blood Sugar(mg/dl)		
Day-0	103.78±0.51	<0.01
Day-180	92.20±0.40	
Fasting Serum Insulin level (mU/ml)		
Day-0	23.18±0.38	<0.01
Day-180	10.13±0.14	
Homa Index		
Day-0	5.89±0.12	<0.01
Day-180	2.28±0.04	

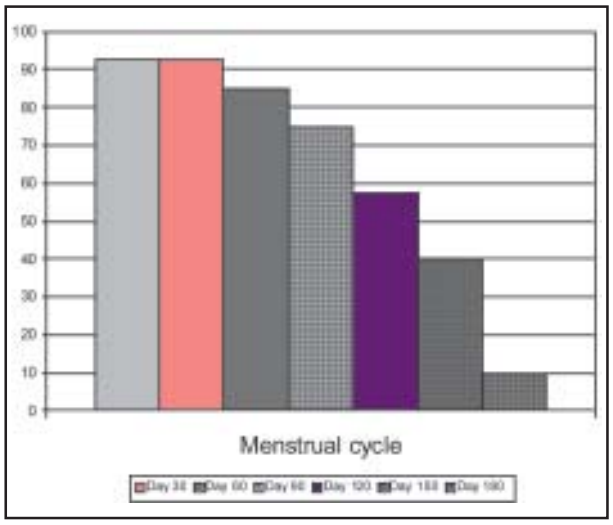

Fig-1: Menstrual Irregularity observed from Day-0 To Day 180.

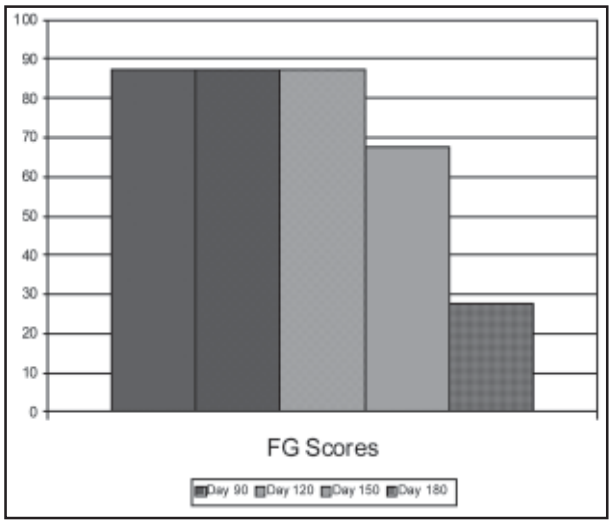

Fig-2: Hirsutism (FGS) observed from Day 0 To Day 180.

was 23.3±0.53 and 21.8±0.55 pre and post treatment respectively.

DISCUSSION

Polycystic ovary syndrome is a leading cause of female factor infertility. A significant number of women with PCOS are overweight. Insulin resistance has long been recognized as a feature of PCOS. It is observed that the high insulin levels exert anabolic effects and modify fat distribution. Metformin helps in normalization of plasma insulin resulting in reduced appetite. It has been shown that weight loss, accompanied by an increase in insulin sensitivity, can improve metabolic and hormonal abnormalities characteristic of the PCOS. The Cochrane library review concluded that metformin treatment of women with PCOS was effective in increasing ovulation rates, fasting insulin and blood pressure in women with PCOS but has less effect on BMI. The primary end point of majority of the studies quoted in this review were related to ovarian function and fertility and non fertility end point were not focussed and hence the validity in this respect was low.[12]

Our present study confirms the positive effects of metformin on menstrual periods and shows that the drug can be administered to obese women to improve hyperandrogenic symptoms such as hirsutism. The beneficial effects of hirsutism in obese women could therefore be due to the restoration of ovulation. Metformin indirectly normalizes the insulin level as shown in our study and also results in a significant reduction in BMI.[13]

There was a significant weight loss between 3 and 6 months after metformin therapy, together with reduction in waist circumference and WHR. Our study showed that metformin not only lowered weight but also maintained it, which is important for PCOS women as they tend to regain weight more easily.[14]

A recent review included 14 selected randomized controlled trial, indicates that metformin treatment of overweight and obese women with PCOS, leads to a significant decrease in BMI as compared to placebo similar to our study, however recommends higher dosage.[15]

Aruna et al[16] has demonstrated that six months of metformin therapy showed significant improvement in BMI, WHR and menstrual irregularity and ultrasonographic features but no change in serum fasting insulin was seen. Santana et al[17] observed that spontaneous menstruation was seen in 81% of patients out of which 67% were obese, with a significant alteration in weight, BMI and WHR.

Obesity clearly aggravates symptoms of PCOS. In a six months study, Metformin lowered weight, HOMA index and FBG significantly in obese women with PCOS, correlating well with our study.[18] Moreover, obese women are prone to early evidence of atherosclerosis.[19] Metformin therapy was thus effective in reducing insulin resistance and hyperandrogenism in women with PCOS.[20]

CONCLUSION

Metformin is a safe and effective drug for the treatment of obese and over weight, women with PCOS. The side effects are minimal and do not significantly effect the compliance. All the parameters assessed in this study showed statistically significant improvement.

Conflict of interest notification page: All the authors do not have any conflict of interest. This study was not supported financially or otherwise by any funding agency or pharmaceutical company. The drug was used on merit as approved by the department. The synopsis was approved by the Board of Advanced Studies and Research University of Karachi. All the participants signed an informed consent administered by the principle investigator.

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Authors Contribution:

AS conceived, designed, collected data, did statistical analysis, writing and editing of the manuscript.
MS did review and final approval of manuscript.
TZ helped in the synthesis of synopsis and editing of manuscript.
SMMA helped in data collection.