

Research Article**Frequency of Efficacy of Metformin in Women
with Polycystic Ovarian Syndrome****Iqra Arif, Maryam Niazi
and Rabia waqar**¹WMO, KRL Hospital, Islamabad²IMO BHU Pai Khel³MO children hospital lahore**ABSTRACT**

OBJECTIVE: to evaluate the efficacy of metformin as a second line monotherapy in cases with polycystic ovarian syndrome(PCOS).

METHODOLOGY: We enrolled 100 cases during the year 2017 from BHU Pai Khel. The sample size was calculated taking reference from previous study⁶ with 95% confidence level, degree of freedom 7% and taking expected efficacy of metformin i.e. 29%.⁶ All diagnosed cases of PCOS, with any BMI and previous history of treatment with clomiphene citrate were the part of this study. Whereas cases with other known systemic disease and treatment for PCOS with other than clomiphene citrate were excluded from the study.

History and physical examination was done and investigations consisting Hormonal profile including day 2nd of menstrual cycle serum FSH, LH, Prolactin, testosterone and mid-luteal phase progesterone and ultrasound examination of pelvis was also done in all cases. Metformin as a monotherapy was started at an oral dose of 500mg/day for one week, then twice a day for another week and then maintained at 1500 mg/ day for 6 months in non- obese women. In obese women the dose was 2000mg in two divided doses. Follow up was done by checking Day 21 Serum Progesterone on monthly visits of the patients to OPD. Ovulation was documented after six months of administration of metformin. The efficacy of Metformin was considered if ovulation (Mid- luteal phase (Day 21) progesterone greater than >25ng/ml to indicate ovulation) was achieved. All findings were recorded on the performa, SPSS-17 was used for data analysis.

RESULTS: CONCLUSION: The use of metformin is for the management of PCO is effective, however, the efficacy is significantly higher in non-obese women than obese PCO women

Key Words: Polycystic ovarian syndrome, metformin, efficacy, obese, non-obese

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is responsible for infertility, hirsutism, and anovulation in reproductive age group females.¹ A dysfunction of hypothalamic function and elevated production of ovarian androgens are the characteristics of PCOS. The incidence of PCOS varies between 4-23% of the cases.²

The mechanism of insulin resistance is not well understood. Alteration in adipokines including resistin may be associated with insulin resistance

in obese cases. Whereas in females with normal BMI, the mechanism is not well cleared, however, it may also be possible that few of the adipose cells are not functioning.³ It may be due to beta-cell dysfunction, increased insulin secretion in response to dietary stimuli, decreased hepatic clearance of insulin and deficient insulin action.⁴

In our country, PCOS is recorded in 17.6% with an increased rate of obesity i.e. 68.5%, hyperinsulinemia was in 59%. Normal BMI was

recorded in 14% cases only, whereas 29.7% cases had 30 BMI and 28.8% cases were having 30-35 BMI.⁵ WHO defined over-weight as $>25\text{kg/m}^2$, obesity was $>30\text{kg/m}^2$.⁶ It is hypothesized that increased BMI exacerbates the underlying insulin resistance in cases with PCOS.⁷

Metformin is considered as a second-generation biguanide. It helps to activate glucose transporters and facilitates in passage of glucose into muscle and hepatic cells, thereby reduces peripheral insulin resistance and lowers the level of serum glucose however, do not stimulate the release of insulin. When it is administered alone, it does not cause hypoglycemia.⁸

Previous data is evident that in non-obese and obese groups 15/17 women (88%) and 5/17 women (29%) ovulated as result and the comparison between the groups was recorded statistically significant.¹⁰

However, we conducted this study with the view to determine the efficacy of metformin in patients with polycystic ovarian syndrome so that metformin may be used in any BMI group. The results would also be helpful for the patients belonging to rural areas where laparoscopy is not available for the management of polycystic ovarian syndrome.

MATERIAL AND METHODS

In this case series, we enrolled 100 cases during the year 2017 from BHU Pai Khel. The sample size was calculated taking reference from previous study⁶ with 95% confidence level, degree of freedom 7% and taking expected efficacy of metformin i.e. 29%.⁶ All diagnosed cases of PCOS, with any BMI and previous history of treatment with clomiphene citrate were the part of this study. Whereas cases with other known systemic disease and treatment for PCOS with other than clomiphene citrate were excluded from the study.

History and physical examination was done and investigations consisting Hormonal profile including day 2nd of menstrual cycle serum FSH, LH, Prolactin, testosterone and mid-luteal phase progesterone and ultrasound examination of pelvis

was also done in all cases. Metformin as a monotherapy was started at an oral dose of 500mg/ day for one week, then twice a day for another week and then maintained at 1500 mg/ day for 6 months in non- obese women. In obese women the dose was 2000mg in two divided doses. Follow up was done by checking Day 21 Serum Progesterone on monthly visits of the patients to OPD. Ovulation was documented after six months of administration of metformin. The efficacy of Metformin was considered if ovulation (Mid- luteal phase (Day 21) progesterone greater than $>25\text{ng/ml}$ to indicate ovulation) was achieved. All findings were recorded on the performa, SPSS-17 was used for data analysis.

RESULTS

In this study, out of 100 cases, 57%(n=57) were between 20-30 years of age whereas 43%(n=43) were between 31-40 years of age, mean \pm sd was calculated as 29.47 ± 6.23 years. (Table No. 1)

Efficacy of metformin in women with polycystic ovarian syndrome was recorded as 63%(n=63) whereas 37%(n=37) had no efficacy. (Table No. 2)

Efficacy according to BMI shows that 12(37.5%) out of 32 cases in obese and 51(75%) out of 68 cases were treated effectively in non-obese patients.

Table 1: AGE DISTRIBUTION (n=100)

Age(in years)	No. of patients	%
20-30	57	57
31-40	43	43
Total	100	100
Mean\pmSD	29.47\pm6.23	

Table 2: EFFICACY OF METFORMIN IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME (n=100)

Efficacy	No. of patients	%
Yes	63	63
No	37	37
Total	100	100

Table 3 EFFICACY ACCORDING TO BMI (n=100)

Efficacy	BODY MASS INDEX	
	Obese	Non-obese
Yes	12(37.5%)	51(75%)
No	20(62.5%)	17(25%)
Total	32	68

DISCUSSION

Various trial reveal the use of Metformin in females with PCOS. Metformin is effective in reducing testosterone levels and in making the menstrual cycle more regular. While Metformin starts to improve the prospects for fertility in few weeks. Women can find weight loss easier when taking Metformin even though it is not a traditional weight reducing agent. One placebo-controlled trail has shown that Metformin is better than placebo in inducing ovulation in women with PCOS. The effectiveness of Metformin has been best demonstrated in obese women and it is likely that women of normal weight would benefit very little from this drug.

The usual dose of metformin is 500 mg three times daily, whether offered as first-line treatment or to women with PCOS who are clomifene resistant. To minimise the mainly gastrointestinal adverse effects, women are commonly advised to take the medication prior to meals and to increase the dosage gradually from once daily, in increments of 500 mg/day each week. Alternatively, it can be prescribed at a dose of 850 mg twice daily to improve compliance. A higher dose (850 mg three times daily) in women with PCOS who are obese does not appear to confer any further benefit.⁹

The current study was planned to determine the efficacy of metformin in patients with polycystic ovarian syndrome so that metformin may be used in any BMI group. The results would also be helpful for the patients belonging to rural areas where laparoscopy is not available for the management of polycystic ovarian syndrome.

In this study, out of 100 cases, 57%(n=57) were between 20-30 years of age whereas 43%(n=43) were between 31-40 years of age, mean±sd was calculated as 29.47±6.23 years, efficacy of metformin in women with polycystic ovarian syndrome was recorded as 63%(n=63), efficacy according to BMI shows that 12(37.5%) out of 32 cases in obese and 51(75%) out of 68 cases were treated effectively in non-obese patients.

Our results are in agreement with the study conducted by Kumari AS and co- workers who

recorded that in non-obese and obese groups 15/17 women (88%) and 5/17 women (29%) ovulated resultantly comparison between the groups was found statistically significant.¹⁰ 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 women with PCOS.¹²⁸ While there is no difference between non-obese and obese patients in some studies,¹¹ others have not been able to demonstrate insulin resistance in lean PCOS women.¹²⁻¹⁴ Obesity clearly aggravates the symptoms of PCOS,^{11, 15} and weight loss is central in the treatment. Crosignani^{PG16} reported that weight loss has been shown to enhance ovulation frequency and improve menstrual cyclicality and endocrine profile.¹⁶ It is also considered of fundamental importance in reducing the cardiovascular risk factors included in the metabolic syndrome. Metformin decreases feeling of hunger during hypoglycaemia,¹⁷ and moderate weight loss is common during metformin treatment, but the conclusions of randomized studies differ with regard to the effect of metformin on weight in PCOS.

Another study by Cynthia R and co-workers¹⁹ concluded that metformin is at least as efficacious in normal and overweight individuals as it is in those who are obese and supported metformin use in nonobese individuals with type 2 diabetes.

The results of the study clarify the comparative efficacy of metformin in non-obese and obese women with polycystic ovary syndrome, though ovulation was significantly higher in non-obese women. So, the metformin may be used in both obese and non-obese women as first line therapy for PCO.

CONCLUSION:

- The use of metformin is for the management of PCO is effective, however, the efficacy is significantly higher in non-obese women than obese PCO women

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