

## ORIGINAL ARTICLE

## Comparison of efficacy of metformin in obese versus non-obese women of PCOS presenting with menstrual irregularities.

Ammara Sanam<sup>1</sup>, Humaira Akram<sup>2</sup>, Alia Nasir-Ud-Din<sup>3</sup>, Durre Shahwar<sup>4</sup>

**ABSTRACT... Objective:** To compare the efficacy of metformin in obese and non-obese women with polycystic ovarian disease presenting with menstrual irregularities. **Study Design:** Quasi Experimental study. **Setting:** Department of Gynecology and Obstetrics, Sargodha Medical College at Maula Bukhsh Teaching Hospital under Dr Fasal Masood Teaching Hospital Sargodha. **Period:** July 2022 to August 2023. **Methods:** Total 156 patients (78 in each group) were selected based on predefined inclusion and exclusion criteria. Patients were randomized in 2 groups according to their BMI. Group A consists of obese women while Group B had non obese women according to predefined operational definition. All patients were given tablet metformin 500mg twice a day and followed up for total of 06 months at every 03 month interval consecutively. On each visit patients were asked about their menstrual cycle regarding duration of bleeding days and length of menstrual cycle. Data entry was done by SPSS version 26. Independent sample t-test was applied to compare mean of numeric data between both groups. A  $p < 0.05$  was considered statistically significant. **Results:** Result showed that metformin was significantly more effective in non-obese women as compared to obese women i-e obese 34.62% vs non obese 50% p value 0.051. **Conclusion:** Results of this study showed that metformin is more effective in treating non obese patients as compared to obese patients in terms of menstrual irregularities.

**Key words:** Efficacy, Irregularities, Metformin, Menstrual, Non Obese, Obese, Polycystic Ovarian Disease.

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### INTRODUCTION

Polycystic ovarian disease is a complex endocrine disorder effecting around 18 percent of young girls of reproductive age worldwide. In Pakistan frequency of PCOS has been found to be 52% which is much higher as compared to women in UK.<sup>1</sup> PCOS is characterized by menstrual irregularities due to oligomenorrhoea or an ovulation, hyperandrogenism and presence of polycystic ovaries on ultrasound. The prevalence of obese patients in PCOS has been shown to be 80% which is two times the rate of obesity in general population.<sup>2</sup> Much of the severity of symptoms in PCOS patients have been proven to be weight dependent. Hence obese patients will manifest a different spectrum of hormonal and metabolic profiles than non-obese PCOS patients, demanding various treatment regimens in two groups.<sup>3</sup>

Management of PCOS depends on the presenting symptoms of patient. For the females presenting with menstrual irregularities, evidence supports

the use of hormonal treatment including oral contraceptives and antiandrogens for regulation of menstrual cycle. Adjuvant drugs in such cases include insulin sensitizers, oral hypoglycemics, and weight loss treatments in case of obese patients requiring weight loss.<sup>4</sup>

Metformin has been advocated to reduce the incidence of diabetes in high risk population and helps in weight reduction of patients with and without diabetes mellitus. When used in PCOS patients, metformin has been shown encouraging results in menstrual cycle regulation and ovulation induction.<sup>5</sup> Various studies have demonstrated positive role of metformin on ovulation, menstrual cycle regulation, insulin sensitivity, body weight, lowering androgen levels and hirsutism.<sup>6</sup> Much of the data is available for obese patients.<sup>7,8</sup> However, to understand the role of metformin in non-obese patients limited data is available which lack methodological rigor. It becomes logical to conduct a study where effect of metformin can be studied both in obese and non-

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obese patients of PCOS presenting with menstrual irregularities to determine the role of metformin in these two distinct groups.

In a study that was a randomized, controlled and double blinded, 56 women with PCOS between the age of 18 and 45 were given treatment for a period of six months. After three months, the patient's treatment was changed to metformin 850mg.<sup>7</sup> Periods occurred at same regular interval for both groups. HDL levels on the other hand, rose ( $p=0.001$ ) in the case group, and the participants lost weight  $p=0.009$  and  $0.047$  respectively). The placebo group saw a weight loss of  $-4.2$  kg (5 -95 percentiles:- 7.0, -1.9), a decrease in fasting plasma glucose of  $0.023(-0.44, -0.01)$  mmol/l, a decrease in insulin of  $-4.17 (-8.10, -0.023)$  mIU/ml, a decrease in the HOMA index of  $-1.50 (-2.53, -0.47)$  mIU/mmol. When compared to placebo treatment, metformin treatment resulted in significant reduction in body weight and fasting plasma glucose as well as HOMA index. Women with PCOS who took Metformin observed improvement in their weight, systolic blood pressure and HDL values according to findings of this study. Metformin had no effect on women who were already a healthy weight, but it did increase insulin sensitivity and lower testosterone levels in women who were overweight.

Management of polycystic ovarian disease is a topic under consideration from so long time, and there are many options for management of PCOS but no final verdict about any drug has been given for its treatment in obese and non-obese patients with menstrual cycle disturbances.<sup>9</sup> The rationale for the use of metformin is derived from mechanistic laboratory studies which demonstrated insulin sensitization in patients predisposed to type 2 diabetes, having insulin resistance. Overall metformin has been used in obese patients with PCOS presenting with menstrual irregularities and subfertility. However, evidence is lacking in use of metformin in non-obese patients with PCOS for same indication. It is expected that apart from weight loss benefits metformin exerts a positive influence in menstrual regulation, hormonal and metabolic profiles of both obese and non- obese patients with PCOS presenting with menstrual irregularities and defining role of metformin in menstrual regulation

in PCOS women with obesity as well as among women with normal BMI.<sup>10</sup>

## METHODS

This is a quasi-experimental study at Department of Gyne and Obstetrics at Maula Bakhsh Teaching Hospital Sargodha.

Study period was 12 months after approval of synopsis from July 2022 to August 2023. The sample size is calculated to be 78 in each group (total 156 patients), with the following parameters. i.e. power of study =95% and level of significance= 5% and by taking expected mean value of frequency of menstrual cycle in obese patients as  $25.3+_{21.7}$  Patients with diagnosed polycystic ovarian syndrome age group 18 to 35 and BMI less than 24.9 in non-obese group and more than 30 in obese group were included. While women wishing for fertility, diagnosed metabolic disorder, hyperprolactenemia, renal disease, liver disease, other causes of menstrual irregularities were not included.

Ethical approval was taken from ethical review committee of Sargodha Medical College letter No. SMC/Prin/739 Dated 14-05-2022 and patients confidentiality was ensured by anonymizing the data.

After approval from the departmental ethical committee, 156 females with polycystic ovarian disease and having complaints of menstrual irregularities, fulfilling the inclusion criteria were selected and enrolled in this study. They were briefed about the procedure and their likely consequences in terms of outcomes. Written consent was taken from them. Medical history was taken, and age was noted. Moreover, demographic details were also recorded on proforma. All the data was kept confidential. Baseline hormonal profile was done. Pelvic ultrasound was done to rule out any pelvic pathology like fibroids, adenomyosis and ovarian cysts.

The patients were allotted in two groups according to their Body Mass Index. Group-A consist of obese women ( $BMI>30$ ) whereas Group B consist of non-obese women according to pre-defined operational definition ( $BMI<25$ ). Initial demographic data of

the included women were recorded. Each patient was asked about details regarding menstrual cycle as defined in the study. Both the groups were prescribed tablet metformin 500 mg in two doses per day for the next 6 months. Common Side effects of Metformin i.e nausea, vomiting, diarrhoea, flatulence, abdominal distension, metallic taste, anorexia, hypoglycemia & hypersensitivity explained to the patients and 3 monthly follow up advised for next 6 months. However, patient were counselled that they can report earlier if they develop any concerning side effects. On each visit, the patients were asked about their duration of bleeding days and length of menstrual cycle. All the data recorded.

Data was collected and analyzed statistically using SPSS 26.0. Numeric data i.e., age, BMI, frequency of menstrual cycles was described by mean and standard deviation. Independent sample t-test was applied to compare the mean of numeric data between both groups. A  $p \leq 0.05$  was considered statistically significant.

**RESULTS**

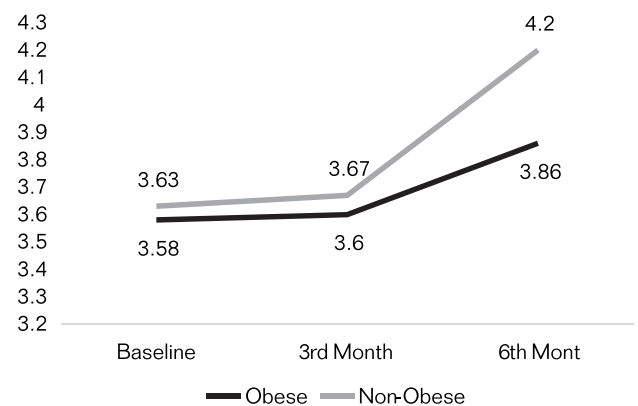
Mean age of women in obese and non-obese group was  $28.10 \pm 3.99$  and  $28.05 \pm 4.01$  years. Age of women in both study groups ranges between 19-34 years respectively. In obese group 68(87.18%) women were married and in non-obese group 69(88.46%) women were married. In obese group 53(67.95%) belong to urban and 25(32.05%) belong to rural areas and on non-obese group 58(74.36%) women belong to urban area and 20(25.64%) women belong to rural 6area. Mean body mass index of women in obese and non-obese women was  $32.41 \pm 0.99$  and  $21.99 \pm 1.37$  respectively. In obese women BMI ranges between 31-35. 40 and among non-obese group BMI ranges between 19.20-24.50.

At baseline mean bleeding days among obese and non-obese women was  $3.58 \pm 1.12$  and  $3.63 \pm 1.05$  days respectively. At 3<sup>rd</sup> month mean bleeding days in obese and non-obese women was  $3.60 \pm 1.09$  and  $3.67 \pm 0.97$  days respectively. At 6<sup>th</sup> month mean bleeding days in obese and non-obese women was  $3.86 \pm 1.16$  and  $4.20 \pm 1.07$  days respectively. At baseline mean cycle length among obese and non-obese women was  $50.67 \pm 7.81$  and  $48.82 \pm 8.07$

respectively- Table-I. At 3<sup>rd</sup> month mean cycle length in obese and non-obese woman was  $50.12 \pm 7.39$  and  $48.61 \pm 8.07$ -Table-II. At this point cycle length was shorter in non-obese women as compared to obese women. AT 6<sup>th</sup> month mean cycle length in obese and non-obese woman was  $47.67 \pm 8.43$  and  $44.19 \pm 10.11$ .

At this point cycle length was shorter in non-obese women as compared to obese women Table-III. Efficacy of metformin was significantly higher among non-obese women as compared to obese women. i.e. Obese: 34.62% vs. Non-obese: 50%,  $p$ -value=0.051 Table-IV.

**FIGURE-1**



**TABLE-I**

Cycle length (days) in Study Groups (Baseline)		
	Obese	Non Obese
N	78	78
Mean	50.67	48.82
SD	7.81	8.07
Minimum	40.00	40.00
Maximum	70.00	70.00

**TABLE-II**

Cycle length in study groups (3 Months)		
	Obese	Non Obese
N	78	78
Mean	50.12	48.61
SD	7.39	8.07
Minimum	40.00	40.00
Maximum	70.00	70.00

TABLE-III

## Cycle length in study groups (6 Months)

	Obese	Non Obese
N	78	78
Mean	47.67	44.19
SD	8.43	10.11
Minimum	30.00	30.00
Maximum	70.00	70.00

FIGURE-2.

## Cycle length in study groups

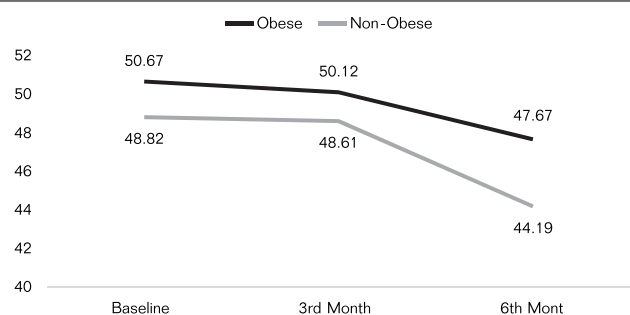


TABLE-IV

## Efficacy of metformin in study groups

	Obese	Non obese	Total
Yes	27 (34.62%)	39 (50%)	66
No	51 (65.38)	39 (50%)	90
Total	78	78	156
p value		0.051	

## DISCUSSION

Hyper-androgenism, irregular menstruation, insulin resistance, low ovulation rates, and infertility are all symptoms of polycystic ovary syndrome (PCOS), and metformin is increasingly being recognized as a viable treatment option.<sup>11,12</sup> Between 30 to 70 percent of women with polycystic ovary syndrome are overweight or obese, and around half of them are centrally obese.<sup>13,14</sup> Obesity may exacerbate PCOS-related comorbidities including type 2 diabetes, hyperlipidemia, and arterial hypertension, as well as the metabolic and reproductive consequences of PCOS like glucose and lipid metabolism, hyper-androgenism, monthly irregularities, and infertility.<sup>15,16</sup>

Metformin has been suggested to lead to a reduction in central obesity and lipid metabolism<sup>17</sup> and it has a greater chance of being effective in obese PCOS,

but not in non-obese subjects.<sup>18</sup> Metformin improves the likelihood of ovulation and helps restore a regular menstrual cycle. Metformin's benefits have been most clearly shown in overweight women, leading some to speculate that it might be ineffective in women with a normal body mass index.<sup>19</sup>

In this study we compared the efficacy of metformin in obese and non-obese women with polycystic ovarian disease presenting with menstrual irregularities. Age distribution of women in this study ranges between 19-34 years. With mean age of women as  $28.10 \pm 3.99$  in obese group and  $28.05 \pm 4.01$  in non-obese group. Chuan Xing in his study reported the age range of PCOS women as 18-40 years with mean age as  $24.37 \pm 4.65$  years respectively.<sup>20</sup> Mugdha Jungari in his study reported the mean age of PCOS women as 24.2 years with age range 16-37.<sup>21</sup>

In another study mean age of PCOS women was reported as  $28.38 \pm 5.53$  years which is similar to the mean age of PCOS women reported in this Study.<sup>22</sup> Age distribution of PCOS women in this study is in line with the local as well as international studies on this topic.

Results of this study regarding efficacy in terms of menstrual regulation showed that metformin was significantly more effective among non-obese women as compared to obese women. i.e. Obese: 34.62% vs. Non- Obese: 50%, p-value=0.051. Metformin has been studied extensively for PCOS, yet there are still several unsolved questions: In PCOS, when is it OK to use metformin? Whether or whether women who are overweight and those who are not.<sup>22,23</sup>

A recently published quasi experimental local study from Karachi assessed the efficacy of metformin in women with and without obesity presenting with PCOs. Menstrual regularity was higher among non-obese participants as compared to obese participants i.e. 62.36% vs. 53.65%, p-value=0.019.<sup>24</sup>

Consistent with the findings of this study higher efficacy of metformin was seen among non-obese patients. i.e. Obese: 34.62% vs. Non-Obese: 50%, p-value=0.051.

Another local research found that among non-obese women with PCOS, 65.2% responded well to metformin treatment.<sup>25</sup> In this study efficacy was seen in 50% of the non-obese women which was slightly lower as mentioned in the above study.

Lean women with PCOS had a considerably greater incidence of menstruation restoration and ovulation compared to their obese counterparts in a Russian research examining the effectiveness of metformin in ovulation induction. Efficacy was determined in terms of cycle length and bleeding days.<sup>26,27</sup> Results of this study is in line with the results of studies mentioned above showing the efficacy of metformin among non-obese patients to maintain menstrual irregularity in terms of cycle duration and bleeding days.

According to Tan S's research, 59% of PCOS patients who were not fat attained monthly regularity, but only 50% of PCOS patients who were obese did so.<sup>28</sup> However, in this study efficacy of metformin for regulating the menstrual cycle among obese and non-obese women is consistent with the findings of Tan S's research, results do differ in terms of their magnitudes in terms of efficacy for both obese and non-obese women.

Hyperandrogenism, anovulation and other reproductive and metabolic diseases have all been linked to insulin resistance, a known hallmark of PCOS. Furthermore, obesity and insulin resistance are not established causal factors for polycystic ovary syndrome, and insulin-resistance may exist in both obese and non-obese women with PCOS. Obesity surgery and behavioral changes may help individuals with polycystic ovary syndrome (PCOS) lose enough weight to restore normal endometrial function and resume ovulation.<sup>29,30</sup>

Contrary findings were reported by Tan S and co-workers in their study they showed that menstrual regularity was achieved in 59% of non-obese PCOS women as compared to 50% of obese females suffering from PCOS.<sup>28</sup> Po-Kai Yang in his study reported that metformin is associated with improvements in menstrual cycle regularity and most hormonal parameters in both obese and non-obese women with PCOS treated with metformin.<sup>31</sup>

Consequently, insulin-sensitizing drugs have been studied for potential use in the treatment of infertility in PCOS-affected women. Glucose intolerance, dyslipidemia, hypertension, central obesity, and insulin resistance are all metabolic abnormalities that may be improved, which in turn may enhance ovulatory function and improve the prognosis for women with PCOS.<sup>29</sup>

Fiza Ali Khan in her study evaluated the efficacy of metformin in obese versus non-obese women with Polycystic Ovary Syndrome (PCOS). As per her findings efficacy of metformin was higher among non-obese women as compared to obese women. i.e. (83.15% vs. 53.65%, p-value<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].<sup>32</sup>

Numerous investigations have shown that metformin has the capacity to not only mitigate weight and metabolic irregularities, but also rectify menstrual cycles, reinstate ovulation, and maybe facilitate conception.<sup>33,34</sup> Research conducted on a cohort of overweight women diagnosed with polycystic ovary syndrome (PCOS) has shown a correlation between endocrine Dysregulation and the manifestation of infertility.<sup>35</sup>

In a comprehensive review and meta-analysis conducted by Yuanyuan Guan, it was shown that metformin has a regulatory influence on sex hormones associated with polycystic ovary syndrome (PCOS) in overweight women. This effect manifests in the promotion of luteinizing hormone production, facilitation of ovulation, and improvement of patients' menstrual cycles.<sup>36</sup> Furthermore, it has the capacity to regulate the release of follicle-stimulating hormone. Several studies have shown a strong correlation between elevated testosterone levels and the presence of aberrant ovarian ultrasonography findings in individuals diagnosed with polycystic ovary syndrome.<sup>37,16</sup>

Metformin may be provided to all women (obese and non-obese) with ovulatory infertility due to the previous discussion and the strong evidence that it improves menstrual irregularities and ovulation in PCOS.<sup>38</sup> Metformin's ability to reduce insulin

levels make it an effective weight-loss aid, and its usage over the course of six months also increases the likelihood of a woman's ovulating normally and experiencing regular periods. However, during the first six months of treatment, metformin should be administered alone.

## CONCLUSION

Results of this study showed that metformin is more effective for treating menstrual irregularity in non-obese women as compared to obese patients.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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The authors declare no conflict of interest.

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#### AUTHORSHIP AND CONTRIBUTION DECLARATION

1	<b>Ammara Sanam:</b> Data collection.
2	<b>Humaira Akram:</b> Concept of study.
3	<b>Alia Nasir-Ud-Din:</b> Data analysis.
4	<b>Durre Shahwar:</b> Drafting.