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Comparison of Metformin and Orlistat in Anovulatory, Overweight and Obese Women with Polycystic Ovarian Syndrome

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ABSTRACT

Objective: To compare the efficacy of Metformin and Orlistat in improving ovulation and reducing body mass index in anovulatory, overweight and obese women with polycystic ovarian syndrome.

Study Design: Quasi-experimental study.

Place and Duration of Study: Gynaecology and Obstetrics Department, Pakistan Air Force Hospital, Lahore Pakistan, Sep 2020 to Apr 2022.

Methodology: Eighty women having polycystic ovarian syndrome with anovulation and body mass index ≥25 were randomized to receive either Metformin (n=40) or Orlistat (n=40). Patients in Group-A received Metformin 500 mg thrice daily; Group-B received Orlistat 120mg twice daily for three months. Patients were also given dietary and lifestyle advice. Ovulatory status and body mass index were measured at baseline and after three months of treatment.

Results: Mean age of women was 26.9±5.1 years, and mean BMI was 29.9±2.57 Kg/m2. Ovulation was restored in 10 women (25%) in Group A and 12 women (30%) in Group B (*p*0.617). Compared to the baseline, women in both groups significantly reduced their BMI (*p*<0.001). However, the difference in the change in BMI of both Groups was not statistically significant (*p*-0.668). 26 women (65%) on Metformin experienced gastrointestinal side effects as compared to 11(27.5%) on Orlistat (*p*=0.001).

Conclusion: Metformin and Orlistat have equal efficacy in improving ovulation and reducing body mass index in women with polycystic ovarian syndrome having anovulation and body mass index ≥25.

Keywords: Metformin, Orlistat, Ovulation, Polycystic ovarian syndrome.

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INTRODUCTION

The most common endocrine and metabolic disorder affecting the women of reproductive age Group is Polycystic Ovarian Syndrome (PCOS).[1] Initially described by Stein and Leventhal in 1935, PCOS is presently defined using the ESRHE/ASRM criteria, also known as Rotterdam criteria, based on the presence of any two of the following three criteria.[2] High rates of Diabetes mellitus, cardiovascular disease, obstructive sleep apnea, non-alcoholic fatty liver disease, and breast and uterine cancer have been reported in these patients.[3,4] Researchers are increasingly becoming aware of the broad spectrum of this condition. Hyperandrogenemia, insulin resistance, LH to FH imbalance, subfertility, cardiovascular disease, obesity, endometrial hyperplasia and carcinoma are some of the features known to this date to be associated with PCOS.[5,6]

Lifestyle interventions such as exercise & weight loss are central to managing anovulatory, overweight and obese patients with PCOS as it helps in the recovery of metabolic and reproductive health.[7,8] One such newer drug is Orlistat which inhibits lipid absorption from the gastrointestinal tract. Orlistat promotes weight loss by inhibiting pancreatic lipase by decreasing fat absorption from the intestine lumen by about 30%. It has been found that by promoting weight loss, Orlistat improves insulin resistance and thus promotes ovulation in these patients.[9]

With the quite remarkable differences in the cost of the two drugs, we conducted this study intending to compare Metformin and Orlistat in terms of two key aspects, i.e., reduction of body mass index (BMI) and improvement in ovulation rates, to understand whether it is justified to use Orlistat instead of Metformin in patients of PCOS in low resource country like ours.

METHODOLOGY

The quasi-experimental study was conducted at the Gynaecology & Obstetrics Department of PAF Hospital Lahore from September 2020 to April 2022. Approval from Hospital Ethical Committee was taken

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(LH/5809/1/P-2). WHO sample size calculator was used to calculate the sample size, taking the population prevalence of obesity in PCOS at 2.6 %.[10]

Inclusion Criteria: Patients aged 18-40 years, already diagnosed with PCOS (Diagnosis of PCOS made according to revised Rotterdam criteria 2003), with BMI ≥25 [BMI was calculated using the formula weight (kg)/Height (m2)] and anovulation (mid-luteal progesterone <20 mmol/L) were included in the study.

Exclusion Criteria: Patients with untreated hypothyroidism, hepatic or renal impairment or hyperprolactinemia were excluded from the study.

Non-probability convenience sampling technique was used. Eighty women presenting to the Gynaecology Outpatient Department fulfilling the inclusion/exclusion criteria were selected. Written/informed consent was taken from all study participants. Patients were divided into two groups randomly using the lottery method. BMI was measured at baseline. Patients in Group-A were started on Metformin 500 mg once a day, and the dose was gradually increased over two weeks to 500 mg three times a day. Patients in Group-B were started on Orlistat 120 mg twice a day from the beginning, and this dose was maintained throughout the study. In addition, patients in both Groups were also advised to take a low-fat diet and perform daily moderate physical activity for 15 to 30 minutes, but how much the patients followed this was not formally assessed. The treatment was continued for 3 months, during which patients came for a monthly follow-up so that compliance could be checked and any adverse effects (in particular gastrointestinal side effects like bloating and abdominal pain) reported. The BMI and Ovulation rates (using mid-luteal phase progesterone cut-off level ≥20mmol/L) were measured after three months of treatment. The reduction in BMI from baseline and ovulation rates were compared between the two Groups.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to explore the inferential statistics. Independent sample t-test and Chi-square test were applied to explore the inferential statistics. The *p*-value of 0.05 or less was taken as significant.

RESULTS

The study included 80 women with PCOS. The mean age of the patients was 26.9±5.15 years, mean BMI of the women at the start of the study was 29.9±2.57 kg/m2. The baseline demographics of study participants are shown in Table-I.

Table I: Baseline Characteristics (n=80)

Baseline Characteristics	Group-A (n=40)	Group-B (n=40)
Age (years)	27.8±5.3	25.9±4.8
BMI (kg/m2)	29.5±2.2	30.3±2.8

Ovulation was restored in 10 women (25%) treated with Metformin (Group-A), whereas in the Orlistat Group (Group-B), 12 out of 40 women (30%) had their ovulation restored. Both Groups were also compared in terms of gastrointestinal side effects like bloating and mild abdominal pain, and these side effects were found to be significantly more in the Metformin Group, where 26 women (65%) experienced these symptoms versus 11 women (27.5%) Orlistat Group (*p*-0.001) as shown in Table-II.

Table-II: Comparison of Ovulation rates and Gastrointestinal side Effects (n=80)

Groups	Group-A (Metformin) (n=40)	Group-B (Orlistat) (n=40)	*p*-value
Ovulation rates	10(25%)	12(30%)	0.617
Gastrointestinal side effects	26(65%)	11(27.5%)	0.001

Compared to baseline, women treated with Metformin had a 0.97±0.65 kg/m2 reduction in BMI, which was statistically significant (*p*<0.001). Women treated with Orlistat had a 0.92±0.40 kg/m2 reduction in their BMI from baseline (*p*<0.001) as shown in Table-III.

Table-III: BMI change in both GROUPS (n=80)

Parameter	Group-A (Metformin)			Group-B (Orlistat)		*p*-value	*p*-value
	Baseline	After 3 months	*p*-value	Baseline	After 3 months		
BMI (kg/m2) (Mean ±SD)	29.5±2.26	28.6±2.2	<0.001	30.2±2.8	29.4±2.7	<0.001	0.668

DISCUSSION

We conducted this study intending to find whether replacing Orlistat with Metformin in managing women with PCOS in our socio-economic set-up is justified. We compared Metformin and Orlistat in their efficacy regarding improvement in spontaneous ovulation and reduction of BMI in patients with PCOS.

After three months of treatment, both drugs improved the ovulation rates, but the difference was not statistically significant. There was a statistically significant reduction in the BMI of patients in both groups as compared to baseline. However, when the Groups were compared with each other, the difference was not found to be statistically significant. Similar findings were reported in a previous study where they found that treatment with either Orlistat or Metformin significantly reduced the BMI of the study participants as compared to baseline (p<0.05); however, no significant difference was noted between Orlistat and Metformin treated patients. They reported superior polycystic ovarian morphology and lipid metabolism improvement with Orlistat in overweight/obese women with PCOS compared to Metformin.[11]

Another study found that 1500mg of Metformin per day for six months, along with lifestyle modification, was effective in inducing weight loss in obese women with PCOS.[12] One study reported in their study that Metformin, in addition to lifestyle, was a critical factor in inducing weight loss and menstrual regulation in patients with PCOS.[13] Our study has also reported the same findings regarding Metformin.

A study concluded that 12 weeks of treatment with Orlistat significantly reduced weight, BMI, waist circumference (p=0.001) and total testosterone levels as compared to baseline in Iranian obese women with PCOS.[14] however this study was performed only on Orlistat, and no comparison with any other drug was made. One study found that Orlistat was more effective than Metformin in reducing body fat (p<0.001) and better tolerated than Metformin.[15] We have also noted in our study that the tolerability of Orlistat was better than Metformin, with 65% of patients on Metformin experiencing gastrointestinal side effects as compared to 27.5% on Orlistat (p=0.001). Another study found that both drugs had similar effects in reducing BMI.[16] This is as per the results of our study. Another study performed a randomized controlled trial to compare the effects of Orlistat and Metformin on ovulation rates and anthropometric measurements in women with PCOS.[17] They reported 33.3% & 23.3% ovulation rates with Orlistat and Metformin, respectively, but the difference was not statistically significant. One study reported a significant reduction in BMI over a period of 3 months with both the drugs as compared to baseline (p<0.001); however, the difference between the groups was not statistically significant (p=1.00).[18] Similar results have been observed in our study with 25% and 30% ovulation rates with Metformin and Orlistat respectively (p=0.617).

We thus found that both drugs have similar efficacy in improving spontaneous ovulation rates and reducing BMI. Until we have evidence for the contrary, in low socio-economic countries like Pakistan, it seems reasonable to continue using the older yet cost-effective drug Metformin in patients who tolerate it. Gastrointestinal side effects are significantly less with Orlistat; we can substitute Metformin with Orlistat in patients who cannot tolerate Metformin due to the GI side effects.

LIMITATIONS OF STUDY

PCOS being a comprehensive clinical spectrum, we have studied the effect of the two drugs on only two aspects, i.e., spontaneous ovulation rates and reduction in BMI. Extensive studies in the future that focus on other aspects of the disease and follow up with the patients for longer durations may better understand the comparative merits of both drugs.

CONCLUSION

Metformin and Orlistat have equal efficacy in improving ovulation and reducing body mass index in women with PCOS having anovulation and BMI ≥25.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

UG & SA: Data acquisition, data analysis, critical review, approval of the final version to be published.

HT: Study design, drafting the manuscript, data interpretation, approval of the final version to be published.

AAK & QN: Critical review, concept, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Azziz R. Polycystic Ovary Syndrome. Obstet Gynecol 2018 ; 132(2): 321-336. https://doi: 10.1097/AOG.0000000000002698.
2. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, *et al*. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 2012 ; 97(1): 28-38.e25. https://doi: 10.1016/j.fertnstert.2011.09.024.
3. Christ JP, Vanden Brink H, Brooks ED, Pierson RA, Chizen DR, Lujan ME, *et al*. Ultrasound features of polycystic ovaries relate to degree of reproductive and metabolic disturbance in polycystic ovary syndrome. Fertil Steril 2015; 103(3): 787-794. https://doi: 10.1016/j.fertnstert.2014.12.094.

4. Bates GW Jr, Propst AM. Polycystic ovarian syndrome management options. Obstet Gynecol Clin North Am 2012; 39(4): 495-506. https://doi: 10.1016/j.ogc.2012.10.001.
5. Spritzer PM, Motta AB, Sir-Petermann T, Diamanti-Kandarakis E. Novel strategies in the management of polycystic ovary syndrome. Minerva Endocrinologica 2015; 40(3): 195-212.
6. Bates GW Jr. Polycystic ovary syndrome: a reproductive and metabolic web of risk, comorbidities, and disease. Fertil Steril 2019; 111(3): 471-472.https://doi: 10.1016/j.fertnstert.2019.01.028.
7. Li Y, Chen C, Ma Y, Xiao J, Luo G, Li Y, *et al*. Multi-system reproductive metabolic disorder: significance for the pathogenesis and therapy of polycystic ovary syndrome (PCOS). Life Sci 2019 ; 228: 167-175. https://doi: 10.1016/j.lfs.2019.04.046.
8. Rocha AL, Oliveira FR, Azevedo RC, Silva VA, Peres TM, Candido AL, *et al*. Recent advances in the understanding and management of polycystic ovary syndrome. F1000Res 2019; 8: F1000 Faculty Rev-565. https://doi: 10.12688/f1000res.15318.1.
9. Sam S. Obesity and Polycystic Ovary Syndrome. Obes Manag 2007 ; 3(2): 69-73. https://doi: 10.1089/obe.2007.0019.
10. Ghandi S, Aflatoonian A. The effects of Metformin or Orlistat on obese women with polycystic ovary syndrome: a prospective randomized open-label study. J Assist Reprod Genet 2011; 28(7): 591-596. https://doi: 10.1007/s10815-011-9564-2.
11. Moghetti P, Tosi F. Insulin resistance and PCOS: chicken or egg? J Endocrinol Invest 2021; 44(2): 233-244. https://doi: 10.1007/s40618-020-01351-0.
12. Panda SR, Jain M, Jain S, Saxena R, Hota S. Effect of Orlistat Versus Metformin in Various Aspects of Polycystic Ovarian Syndrome: A Systematic Review of Randomized Control Trials. J Obstet Gynaecol India 2018 ; 68(5): 336-343. https://doi: 10.1007/s13224-018-1140-6.
13. Ecklund LC, Usadi RS. Endocrine and reproductive effects of polycystic ovarian syndrome. Obstet Gynecol Clin North Am 2015 ; 42(1): 55-65. doi: 10.1016/j.ogc.2014.09.003.
14. Zhao YX, Wang LJ, Gong FY, Pan H, Miao H, Duan L, *et al*. [Effects of Orlistat and Metformin on metabolism and gonadal function in overweight or obese patients with polycystic ovary syndrome]. Zhonghua Nei Ke Za Zhi 2021; 60(12): 1165-1168. Chinese. https://doi: 10.3760/cma.j.cn112138-20210302-00171.
15. Li Y, Tan J, Wang Q, Duan C, Hu Y, Huang W, *et al*. Comparing the individual effects of Metformin and rosiglitazone and their combination in obese women with polycystic ovary syndrome: a randomized controlled trial. Fertil Steril 2020 ; 113(1): 197-204. doi: 10.1016/j.fertnstert.2019.09.011.
16. Naderpoor N, Shorakae S, de Courten B, Misso ML, Moran LJ, Teede HJ, *et al*. Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. Hum Reprod Update 2015; 21(5): 560-574. https://doi:res 10.1093/humupd/dmv025.
17. Salehpour S, Hosseini S, Nazari L, Saharkhiz N, Zademodarres S. Effects of Orlistat on serum androgen levels among iranian obese women with polycystic ovarian syndrome. JBRA Assist Reprod 2018 ; 22(3): 180-184. https:doi: 10.5935/1518-0557.20180033.
18. Ruan X, Song J, Gu M, Wang L, Wang H, Mueck AO, *et al*. Effect of Diane-35, alone or in combination with Orlistat or Metformin in Chinese polycystic ovary syndrome patients. Arch Gynecol Obstet 2018 ; 297(6): 1557-1563. https://doi: 10.1007/s00404-018-4762-0201320.

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