ORIGINAL ARTICLE

Role of Orlistat Combined With Life Style in the Management of Obese Patients with Polycystic Ovarian Syndrome

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ABSTRACT

Background: Obesity is frequently present in women with polycystic ovarian syndrome (PCOS) and aggravates insulin resistance (IR) and hyperandrogenemia.
Aim: To compare the effects of orlistat combined with life style changes in obese women as compared to lifestyle changes only, on ovulation rate and decrease in body mass index, waist circumference and hyperandrogenemia.
Design: Randomized Control Trial.
Setting: Department of Obs/Gynae Shalamar Hospital Lahore.
Methods: Cohort of 45 women with diagnoses of PCOS and BMI ≥ 30 were divided in two groups. Group A (n=30) were instructed to receive cap orlistat 120 BD + low caloric diet exercise and Group B (n=15) will be followed low caloric diet and exercise only for 12weeks.
Outcome measures: The primary outcome measure were occurrence of ovulation as detected by Day-21 serum progesterone (> 4ng/ml) and fall in BMI. Secondary outcome measures were include changes in hip and waist circumference and changes in androgen profile as measured as free androgen index.
Results: Study Depicted significant reduction in BMI and waist circumference as well as ovulation rate of 69.02% with Orlistat over period of 3months as compared to diet only group with ovulation rate of 9.09%. FAI was significant (P=.001) in orlis group as compared to diet group.
Conclusion:: Orlistat is safe antiobesity drug with minimal side effects and can achieve significant reduction in BMI and waist circumference with 70% ovulation rate over shorter period of time Larger studies are required to study effect of orlis on lipid profile and insulin resistance.
Keywords: PCOS, Obesity, Orlistat, Free Androgen Index (FAI).

INTRODUCTION

Polycystic ovarian syndrome is the most common endocrinopathy seen in 15% of women of reproductive age[1]. Obesity is frequently present in women with polycystic ovary syndrome (PCOS) and appears to play an important role in the manifestation of this syndrome[2]. Obesity contributes to the pathogenesis of pivotal characteristics of PCOS including infertility, hyperandrogenemia and insulin resistance (IR)[3]. The prevalence of PCOS in South Asian women especially in Pakistani women is much higher (52%) as compared to white population (20-25%) in UK[4]. South Asian PCOS are more obese as compared to Caucasians they have greater insulin resistance and more severe symptoms of syndrome[5]. Since obesity exacerbates the signs and symptoms of insulin resistance, weight loss can improve both metabolic and endocrinal profile of PCOS[6]. In over weight and obese woman with PCOS, life style changes achieved mainly by dietary changes and increase in physical activity represents first line treatment and these life style changes alone have shown to be highly effective in improving ovarian function[7].

However weight loss is frequently small with life style changes alone and many women eventually gain weight[6].

The only currently available antiobesity agent used in most countries is orlistat. It is gastric and pancreatic lipase inhibitor that decreases fat absorption from intestinal lumen by 30%[8] which does not have systemic adverse effects and appears to exert beneficial effects not only on body weight but also on other cardiovascular risk factors, including types 2 diabetes mellitus, hypertension and dyslipidemia[9].

There were no studies to estimate the ovulation rate with orlistat. However since orlistat is weight losing drug with only minimal systemic absorption (<1%)[8]. It was assumed that any effect for this drug would be a result of weight loss alone and not due to direct ovarian effect. Ovulation rate for orlistat may therefore be similar to those reported with weight losing programs consisting of dietary changes and physical activity alone.

Such studies have shown that a 10% reduction in body mass using a weight loss program can result in 92% ovulation rate over a course of 6 months[7]. A 10% drop in BMI over a period of 12 weeks has been demonstrated to be achievable with orlistat.[10] It is therefore assumed that over a 12week period orlistat could show a similar ovulation rate to that achieved though 10% drop in BMI using weight loss programm.

The sample size was therefore calculated with anticipation of 70% ovulation with orlistat. At power of 80% and & error of 0.05 this yielded a sample size of 20 patients in each arm. It is suggested that orlistat is better as weight reducing agent because of its better tolerability and compliance[11].

The aim of present study is to compare the effects of orlistat and life style changes in obese women with PCOS, on anthropometric measurement by changes in waist circumference and BMI, on ovulation and hyperandrogenemia.

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MATERIAL & METHODS

It was a randomized control trial conducted at department of Obs/Gynae Shalamar Hospital Lahore. Randomization was done through separate randomization tables based on group using drug and other group only life style changes. Study was carried over a period of 12 weeks for each patient. We recruited 30 patients in group A and 15 in group B Clue of inducting lesser patient in cohort group was taken from a larger study where author involved 101 patients with orlis in obese PCO patients and 29 control with matched BMI and normal ovulating cycle.[12]

Sample technique was non probability purposive sampling and inclusion criteria includes.

- Women who are diagnosed suffering from PCOS
- BMI ≥ 30kg/m^2
- Age between 18-40years
- Not taking any medication that alters hypothalamic pituitary axis

Exclusion Criteria includes

- Patients with hepatic or renal impairment
- Malabsorption syndrome, cholestasis
- Pregnancy, breast feeding mothers

The duration of study was from 22nd September 2016 to 30th September 2017. Patients were recruited from Shalamar Hospital Gynaecology outpatient Department after giving written consent. The diagnosis of PCOS was made according to the revised European society for Human Reproduction and Embryology/American society for reproductive Medicine (ESHRE/ASRM) Rottermdam criteria 2004 with presence of at least two of the following three features after exclusion of other etiologies through history, clinical examination and laboratory investigations if needed, oligomenorrhoea or amenorrhoea, anovulation, clinical and biochemical features of hyperandrogenism (Hirsutism, Acne) and ultrasound finding of polycystic ovaries that is presence of 12 or more follicles in each ovary measuring 2-9mm in diameter and/or increased ovarian volume >10ml.

In all women weight, height and waist circumference (W) which was measured as the smallest measurement between iliac crest and 12th rib. Hip circumference (H) was measured at the level of widest diameter around the buttocks. W to H (WHR ratio was calculated by dividing W by H. The BMI was calculated by dividing weight (in Kg) by height in square meters. It consisted hypocaloric balanced diet of 1400kcal/day with 5-10%fats. A printed diet plan was given to the patients.30minutes/day of moderate intensity aerobic exercise (e.g.,) brisk walk, cycling or tread meal.

Baseline and 12weeks blood sample were for serum LH, progesterone Testosterone & SHBG were taken drawn in both groups for following blood levels. All the tests were performed in our laboratory by chamiluminescence immunoassay (CLIA).

Baseline and day 21 serum progesterone level >4ng/ml as taken sign of ovulation. Total testosterone >3.5nmol/L and free androgen index will be calculated be following formula (Total testosterone x 100/SHBG) >5nmol/L are taken as sign of hyperandrogenemia. SHBG 15-120nmol/L & LH level = 10miu/ml as normal level.

All information was recorded in predesigned Performa after approval of hospital ethics committee and informed consent of patient was taken. The primary outcome measure was occurrence of ovulation as detected by Day-21 serum progesterone (>4ng/ml) and fall in BMI. Secondary outcome measures will include changes in waist circumference and changes in androgen profile as measured as free androgen index. Statistical analysis will be performed with statistical package SPSS(version 17). Qualitative variable will be reported as mean ± SD Changes between baseline and end of treatment of will be assessed by Pearson correlation. Quantitative variable will be compared by student t test. In all cases a P Value, 0.05 will be considered significant.

RESULTS

The No. of patients recruited were 45, there were 8 drops out, 4 in treatment arm and 4 in the controls. There was only 2 cases of minor gastrointestinal side effect. Drops out were mainly due to noncompliance. There were 26 patients in the study (Group A) and 11 in the control (Group B). Table I shows baseline demographic and hormonal profile of both study and control. Both groups (A & B) patients were obese with BMI of 33.27 and 32.56 respectively, Group A has irregular periods in 53.8% and Group B had 91% while androgenic. Symptoms were more in group A 96.2% as compared to group B 72.7% where as presence of polycystic ovaries in both groups was comparable, 88.5% and 91% respectively. SHBG was lower 25.02 in orlis group as compared to 35.52 in diet only group. Free androgen index was significantly higher in group A (P=.03). FAI 12.71nmol/L as compared to 3.68 in group B.

Table B Show changes in anthropometric and hormonal profile after 3months of study. BMI reduced significantly in both groups but it was highly significant in group A (P.000). Similarly waist circumference reduction was more significant in group A taking orlis. (P=.0000). Menstrual cycle irregularly improved in both groups, but it was not significant. While testosterone level fell more in study cases then control but the fall was not significant. Whereas level of SHBG rose significantly (P=.0002) in orlistat group and this led to fall in FAI significantly (P=.001) in orlistat group. Table III depicts that in orlistat group 69.2% patient elicited ovulation as compared 9.09% in Diet only group. This is highly significant (P value.0001). Table IV shows the predictors of responders. Although patients in both groups were obese, responders had less BMI 32.31 as compared to 35.38 in non responders. While S. Testosterone and LH did not have any Influence. FAI was high in non responders.

Table 1: Baseline demographics and hormonal profile of both groups

Parameters	Study Groups (n=26)	Control Groups (n=11)	P-Value
Age (Years)	26.77 ± 5.57	23.82 ± 4.35	0.13
BMI (Kg/M^2)	33.27 ± 5.63	32.56 ± 4.72	0.71
Waist Circumference (cm)	103.44 ± 10.08	98.36 ± 10.02	0.17
Hip Circumference (cm)	115.57 ± 9.05	115.0 ± 12.85	0.84
Irregular periods	14 (53.8%)	10 (91%)	0.06
Androgenic Symptoms	25 (96.2%)	8 (72.7%)	0.07
Polycystic Ovaries	23 (88.5%)	10 (91%)	1.000
Serum LH	7.12 ± 4.27	6.81 ± 3.8	0.84
Serum Progestron	0.48 ± 0.12	0.17 ± 0.08	0.78
Serum Testosteron	1.97 ± 1.52	1.15 ± 0.54	0.09
Serum SH BG	25.02 ± 23.80	35.52 ± 23.48	0.23
Free Androgen Index	12.71 ± 3.22	3.68 ± 2.35	0.03*

P Value < .05 Significant

Table II: Comparison between groups in anthropometry and hormonal profile after 3 months of treatment

Parameter	Pre-treatment	Post-treatment	P-Value
BMI Cases	33.26 ± 5.6	30.65 ± 5.0	0.000*
Control	32.55 ± 4.72	30.95 ± 5.08	0.003*
Waist Circumference Cases	103.67 ± 10.12	94.59 ± 12.76	0.000*
Control	98.36 ± 10.03	92.36 ± 9.1	0.002*
Testosteron Cases	1.97 ± 52	1.73 ± 1.26	0.417
Control	1.15 ± 0.54	1.14 ± 0.61	0.953
SH BG Cases	25.03 ± 23.70	31.70 ± 22.9	0.002*
Control	55.97 ± 68.41	39.32 ± 25.21	0.35
Free Androgenic Index Cases	11.2 ± 7.11	6.5 ± 5.51	0.001*
Control	3.68 ± 2.35	3.56 ± 1.35	0.779

P Value < .05 Significant

Table III: Evidence of ovulation as detected by serum progestron in both groups

Groups	Responders	Non-responders
S. Progestron	> 4ng/ml	< 4ng/ml
Cases	18 (69.2%)	8 (31.1%)
Control	1 (9.09%)	10 (90.9%)
Total	19	18

P Value 0.001 (Significant)

Table IV: Predictors of response (ovulation) the table shows the anthropometric and endocrine baseline characteristics

Parameters	Responders	Non-responders	P-Value
BMI	32.31 ± 5.08	35.38 ± 6.58	0.21
Waist Circumference	104.80 ± 9.54	101.1.3 ± 11.57	0.41
S. Testosteron	2.1 ± 1.90	1.77 ± 0.80	0.65
FAI	9.80 ± 6.99	14.40 ± 6.71	0.13
LH	7.36 ± 4.1	6.57 ± 4.90	0.672

P Value < .05 Significant

DISCUSSION

Orlistate produced significant reduction in weight loss over 3months period as compared to control. Previous studies comparing orlistat and metformin have also shown significant weight reduction by orlistat than metformin[13].

However metformin can produce weight loss but this advantage is limited by gastroenterology side effects. Orlistat is preferable as weight reducing because it has better compliance and tolerability. Patient should take low fat diet to prevent steatorrhoea[11].

Our study showed ovulation rate of 69.2% as compared to 9.09% in diet only group. Two patients also conceived in group A. As predicted a 10% drop in BMI can result in ovulation rate of 70% - 90%. It was achievable over a period of 3months as compared to diet only group which takes 6months[10].

Out study resulted in 8% loss of weight. Some previous studies have shown smaller weight reductions, ranging between 3.9% and 5.7%13). In those studies patients were asked not to modify their diet during orlistat treatment. In addition, advice regarding exercise was not provided in most studies.

As secondary outcome improvement in orlistat group, menstrual irregularity reduced from 53.8% to 23.1% as well as androgenic symptoms such as acne and hirsutism from 96.2% to 69.6% improved in both group but results were not significant. SHBG rose significantly in orlis group leading to significant reduction in free androgen index. Although S. Testosterone showed if a fall but it was not significant.

This is in agreement to studies by Metwally et al 2009 and Tayagopal et al 2005, when they demonstrated significant fall in free androgen index. Patients who ovulated (responders) had lower BMI and free androgen index.

Similar study performed in Turkey[15,16] and Oman concluded that total testosterone and AFI are effective in diagnosing hyperandrogenism although it is reported AFI being the superior test. My study also demonstrates the effectiveness of AFI to determine the hyperandrogenemia in southasians. As more than 90% of plasma testosterone is bound to SHBG, So AFI level in plasma is a more sensitive indicator of hyperandrgenism than total testteron[17]. In our study group A had significant reduction in weight which had to increase in SHBG so causing significant fall in orlis group. When examining the clinical and biochemical parameters as predictors of success those patients who had less BMI and waist circumference and lower AFI ovulated significantly more. As it is already known by studies that decrease in BMI results in improvement in ovarian function. [7,18,] Metwally et al 2009 in this study found decrease in LH as a significant predictor of success, In our study both groups had comparable LH level in responders and non responders 7.36iu/l and 6.57iu/l respectively and weight loss did not led to any further fall in LH level. Limitations of our study are that sample size was smaller, and it could not be double blind because control group had to buy the medications. Patients were very non cooperative, although they were called every 4weeks to ensure the compliance, many had financial issues. Pharma Industry should reduce the cost of this useful drug so that more patients can benefit from this.

CONCLUSION

Orlistat is safe antiobesity drug with minimal side effects and cane achieve significant reduction in BMI and west circumference with 70% ovulation rate over shorter period of time Larger studies are required to study effect of orlis on lipid profile and insulin resistance

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