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GONADAL PHYSIOLOGY AND DISEASE

The effects of metformin or orlistat on obese women with polycystic ovary syndrome: a prospective randomized open-label study

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Abstract
Purpose Comparing the effects of metformin or orlistat on hormone, lipid profile and ovulation status in obese women with polycystic ovary syndrome.
Methods A total of 80 women were prospectively recruited to receive either metformin (n=40) or orlistat (n=40). Weight, BMI, waist, serum LH, total serum testosterone and lipid profile were assessed at baseline and after 3 months. The subjects' ovulatory status was assessed after 3 months.
Results There was no significant difference in ovulation between the two treatment groups (30% vs 15%). Treatment with either drug showed a significant decline in body weight, BMI (Body Mass Index), and waist circumference, but the degree of decline in both groups was the same. Patients who were treated with orlistat, showed a significant reduction in total testosterone and serum lipid. Women in metformin group showed a significant reduction in serum LH.
Conclusions Both metformin and orlistat showed a similar effect on weight loss and ovulation rates.

Capsule Metformin and orlistat show a similar effect on weight loss and ovulation rates in obese PCOS patients.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility [1, 2] which can be seen in approximately seven to eight percent of women of reproductive age [3]. It is a very heterogenous syndrome both in its clinical presentation and laboratory manifestations. The majority of women (75% to 100%) [4–6] with anovulation due to PCOS have menstrual irregularities, usually oligomenorrhea or amenorrhea, associated with clinical and/or biochemical evidence of hyperandrogenism. In addition to abnormal morphology of the ovary [7], increased ovarian production of androgens [8], hyperinsulinemia. is present in about 80% of obese women with PCOS [9] and 50–70% of all women with PCOS [10].Hyperinsulinemia and insulin resistance may contribute to increased risk of developing type II diabetes, hypertension and the adverse cardiovascular risk [11]. Hyperinsulinemia is more strongly associated with anovulation than any other feature of the syndrome. This association between PCOS and damaged insulin action has been indicated in previous studies, which describe insulin resistance as an integral feature of PCOS [12, 13]. Hyperinsulinemia increases ovarian androgen secretion resulting in abnormal ovarian follicular development and disturbed menstrual activity [14, 15]. These pathophysiological mechanisms and the strong relationship between hyperinsulinemia and anovulation have prompted trials evaluating the effect of

insulin sensitizing agents like metformin on ovulation rate in PCOS and/or obese patients. Obesity that is about to reach epidemic proportions in many countries, is a common problem in modern societies [16, 17]. An excess of body fat among women with PCOS accentuates insulin resistance and its associated clinical sequelae [18, 19]. Since obesity exacerbates the signs and symptoms of insulin resistance, weight loss can improve ovarian function and the associated hormonal abnormalities [20, 21]. Therefore, weight loss should be the first line treatment in obese women with anovulatory infertility associated with PCOS. Several modes of pharmacological treatment have been mentioned for these women as well. Metformin is an oral biguanide antihyperglycemic drug whose positive effects on reducing hyperinsulinemia and improving the metabolism situation have been proved by various studies. Besides these metabolic effects, metformin seems to have a significant impact on ovulation rates [14, 22]. On the other hand, orlistat which is an effective and irreversible inhibitor of gastric and pancreatic carboxylester lipase, can inhibit lipid absorption. Orlistat is an antiobesity drug which promotes loss of weight by decreasing fat absorption from the intestine lumen by about 30% [23, 24].Because weight loss is associated with improvement in ovarian function in PCOS women, it seems that orlistat may increase ovulation rate as well.

Previous studies showed the effects of 3 month use and 6 month use of metformin on ovulation. Short term use of metformin resulted in 25% ovulation [25]. In another short term study, 12 week use of metformin led to 73% ovulation [26].But 6 month use of metformin resulted in 62.9% [27], 55.4% ovulation [28].

The other randomized studies have also tried to compare the effects of orlistat and metformin in obese PCOS patients, but they have not reported the ovulation rate and had a small number of cases [29, 30]. In a randomized study the effects of orlistat and metformin were compared in obese anovulatory patients regardless of the presence or absence of PCOS and the results showed no significant difference in ovulation rate between orlistat and metformin [31].

The aim of this study was to compare the effect of metformin and orlistat on ovulation, total testosterone, LH level, lipid profile, weight, BMI (Body Mass Index) and waist circumference in obese PCOS patients.

Materials and methods

Subjects

The study was approved by the Ethics committee of Research and Clinical Center for Infertility, Shahid Sadughi University of Medical sciences, Yazd, Iran. Written informed consent was obtained from all of the cases before enrolling the study. Subjects were recruited from the gynecology outpatient clinic between December 2008 and November 2009. Women were included in the study if they met all of the following conditions: diagnosed to have PCOS, aged between 18–40, BMI ≥30 kg/m^2, no history of taking medication or dietary modification currently or for the preceding 3 months. The diagnosis of PCOS was made according to the revised 2003 European Society for Human Reproduction & Embryology / American Society for Reproductive medicine (ESHRE / ASRM) Rotterdam Criteria (Rotterdam ESHRE / ASRM—sponsored PCOS consensus workshop Group, 2004) with the presence of at least two of the following three features after exclusion of other etiologies: oligo- or anovulation, clinical and/ or biochemical hyperandrogenism and ultrasound finding of polycystic ovaries (presence of 12 or more follicles in each ovary measuring 2–9 millimeter in diameter, and / or increased ovarian volume (>10 ml). BMI was calculated using this formula: weight (kg) / height ^{2} (m). The exclusion criteria were eumenorrheic PCOS, presence of impaired fasting glycemia, untreated hypothyroidism, renal or hepatic impairment, hyperprolactinemia and nonclassical 21 – hydroxylase deficiency.

Study design

This was a randomized, open – label, parallel study to compare a 3 month treatment with metformin or orlistat. Randomization was performed using random number table. The dose of metformin was increased step – wise, from 500 mg once daily for the first week to 500 mg twice daily for the next week, and to 500 mg three times daily for the remaining study period .The dose of 120 mg orlistat was taken three times daily and the dose remained constant throughout the study period. Clinical and biochemical assessments were performed at random and at the end of the 3-month period. Weight, BMI and waist circumference were measured. Endocrine profile including baseline serum LH and total testosterone performed on the second day of a spontaneous cycle or progesterone—induced bleeding using an ELISA plate reader (TECAN sunrise absorbance reader; Tecan Austria GmbH, Austria). Lipid profile including total cholesterol and triglyceride was measured using a Vitalab Selectra E analyzer (Vital Scientific, United Arab Emirates).

In this study, the primary outcome was the occurrence of ovulation which was evaluated by serum progesterone level (>4 ng/ml) on day 21. Secondary outcomes were considered as change in weight, BMI, waist circumference, hormonal and lipid profile.

Statistical analysis

The effect of treatment was firstly evaluated by computing the percentage of changes from baseline in all variables

Table 1 Ovulation rate in both treated groups

Groups	Metformin (n=40)	Orlistat (n=40)	P-value
Ovulation rate	30% (12/40)	15% (6/40)	0.108

studied. Secondly, the percentage of changes which had been observed for each variable in both groups was compared, thus negating the differences in the baseline values of the two groups. Statistical analysis was performed using Statistical Package for the Social Sciences, version 13. Data are presented as mean ± SEM. Comparisons within each group, regarding the percentage of changes from baseline were performed using the paired t test for normal distributed variables (BMI, waist, testosterone) and wilcoxon signed ranks test for abnormal distributed variables (weight, LH, cholesterol, triglyceride). The chi-square test was used to compare ovulation rate between groups. Student t test was used to compare the percentage of changes of normal distributed variables between two groups and Mann-whitney U test was used to compare the percentage of changes of abnormal distributed variables between two groups. A P value of <0.05 was considered statistically significant.

In order to detect a clinical meaningful difference of 28% with a power of 80% (α=0.05) a sample size of (n= 40) in each group was needed.

Results

Eighty women with PCOS were screened. The mean age was 27±4.92 and the mean body mass index was 33.68± 4.2 kg/m^2. All subjects completed the three-month study period. Three patients taking the dose of 1500 mg/day in metformin group showed symptoms of nausea and mild abdominal pain and for these patients, dose reduction was needed. In two patients the gradual increasing of the dose up to 1500 mg/day was tolerated, while in another patient dose of tolerance was 1000 mg/day. Two patients in orlistat group showed cramping and oily stool during the first 2 weeks of treatment but it was not necessary to stop treatment or reduce the dose of drug.

The ovulation rate was 30% in patients treated with metformin and 15% in orlistat group (P=0.108) (Table 1).

Comparing with baseline, treatment with orlistat resulted in a significant reduction in weight, BMI, waist circumference, total testosterone, total cholesterol, and triglyceride.

Treatment with orlistat resulted in 3.9% reduction in serum LH, but the difference was not significant (Table 2).

In comparison to the baseline, treatment with metformin resulted in a significant reduction in weight, BMI, waist circumference, serum LH and triglyceride.

Treatment with metformin also resulted in a reduction in total testosterone and total cholesterol level but the differences were not significant (Table 2).

The overall comparison between the two groups at the end of treatment did not reveal any significant differences in the orlistat and metformin treatments except for the cholesterol level, in which orlistat had a greater effect (Table 2).

Discussion

It has been shown that treatment with metformin is effective for amelioration of the hormonal and metabolic consequences in PCOS women [32, 33]. In this study we compared the effect of metformin, an insulin sensitizing agent, with

Table 2 Subject characteristics at the baseline and after 3-month treated period

Parameters	Orlistat (n=40)				Metformin (n=40)				
	Baseline	3 months	Changes (%)	P-value*	Baseline	3 months	Changes (%)	P-value*	P-value** Metformin vs. Orlistat
BMI (kg/m^2)	34.88±4.90	33.24±4. 19	−4.48±.47	<001	32.49±3.06	31.03±3.43	−4.55±.70	<001	n.s
Waist (cm)	113.25±11.96	110.85±11.86	−3.88±.40	<001	104.15±9.22	100.80±9.83	−5.04±.67	<001	n.s
Weight (kg)	87.05±13.62	83.47±11.80	−3.88±.40	<001	79.80±9.63	75.85±10.21	−5.04±.67	<001	n.s
LH (mIU/ml)	7.92±4.42	7.02±5.90	−3.9±10.32	.056	6.58±4.81	5.25±3.77	−5.7±8.58	.008	n.s
Testosterone (ng/ml)	0.80±0.23	0.63±0.22	−19.37±3.52	<001	0.78±0. 44	0.66±0.34	−17.30±5.30	0.053	n.s
Cholesterol (mg/dl)	215.05±38.42	194.30±47. 04	−9.39±2.43	.001	169.80±27.97	165.85±24.36	−1.54±1.76	. 30	.023
TG (mg/dl)	194.10±70.76	155.85±65.75	−15.26±4.93	.001	133.95±41.30	108.50±52.51	−19.97±3.40	<.001	n.s

Data are presented as mean ± SEM. All serum results are obtained from fasting variables

BMI, body mass index; LH, luteinizing hormone; TG, triglyceride

P* for paired t-test and Wilcoxon signed rank test; p** for student t-test and Mann-whitney U test

orlistat, an antiobesity drug, on ovulatory status in obese PCOS patients and found that both drugs have a similar effect on ovulation rate. This is the second study which compares the effects of these drugs on ovulation rate. In the first study performed by Metwally [31], the effects of these drugs were assessed in obese women, regardless of the presence or absence of PCOS and the results showed a non significant increase in ovulation rate by metformin.

Orlistat is an antiobesity drug, which has been shown to produce a significantly greater degree of weight loss than metformin [30]. Our study in agreement with Metwally study [31]showed that metformin has the same effect as orlistat on weight loss. This may be the result of decreased appetite caused by metformin leading to decreased food intake which has been shown in previous studies [34, 35].

The current study, like previous ones [36–38] indicated that treatment with orlistat led to a significant reduction in testosterone concentration. Orlistat is a weight loss drug with minimal systemic absorption [24] and therefore any effect of this drug is a result of weight loss and not the direct effect on ovaries. Treatment with metformin caused a significant reduction in body weight and BMI, but a non significant reduction in testosterone. In another study, metformin reduced weight and waist circumference but did not affect testosterone level [39]. Jayagopal reported that metformin-treated subjects presented the same reduction in testosterone concentration as cases treated with orlistat, although the weight loss was much less in metformin group than orlistat—treated patients [30]. The effects of metformin treatment in terms of hyperandrogenemia are various. Whereas some investigators have reported decreased testosterone levels after metformin treatment [40–42], these effects were not confirmed by other trials [22, 43]. The positive effect of metformin on ovulation can occur without additional metabolic changes and weight reduction [43, 44].

In this study, treatment with metformin reduced serum LH level. This finding is consistent with previous studies in which metformin therapy decreases serum LH level [45, 46]. In our study treatment with orlistat did not significantly reduce LH level. Weight reduction in PCOS has been reported to improve hyperinsulinemia [36, 47–49], and reduce serum LH level [50]. Metformin and the other insulin sensitizing agents interact on different levels of insulin physiology. Since these drugs act via different mechanisms, it has been suggested that the reduction of insulin may reduce directly or through unknown mechanisms, the pituitary LH synthesis and discharge [51, 52], whereas orlistat acts indirectly through reduction of weight. It seems that longer treatment with orlistat is needed to reach a significant reduction in serum LH level.

Treatment with orlistat in this study resulted in a significant decline in total serum cholesterol and triglyceride. Metformin treatment caused a significant reduction in serum triglyceride but not cholesterol and it is in agreement with other studies in which metformin, reduced weight and serum triglyceride [39].

Women in orlistat group had 15% ovulation rate which is much lower than the previous studies in which significant weight loss by life style and diet modification for a longer time period (6 months) resulted in 60–70% ovulation [21, 37].

In summary our study suggests that both metformin and orlistat cause similar reductions in weight, BMI, and waist circumference. The ovulation rate is higher in metformin treated patients although the difference is not statistically significant. More studies with longer duration of treatment are needed to compare the effects of these drugs on ovulation rate.

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