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SYSTEMATIC REVIEW/META-ANALYSIS

Effect of Orlistat Versus Metformin in Various Aspects of Polycystic Ovarian Syndrome: A Systematic Review of Randomized Control Trials

Soumya Ranjan Panda[1] · Madhu Jain[1] · Shuchi Jain[1] · Riden Saxena[1] · Smrutismita Hota[2]

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About the Author

Soumya Ranjan Panda He is presently working as a senior Resident in the Department of Obstetrics and Gynecology, IMS, BHU, Varanasi, UP.

Abstract

Background Polycystic ovarian syndrome (PCOS), a commonly prevalent endocrinopathy among reproductive age group women, is most often associated with obesity. Increased insulin resistance appears to be the central pathophysiologic mechanism responsible for various complications of PCOS. This makes 'weight loss' as the first-line treatment approach in PCOS. So various trials have tried to compare metformin (an insulin-sensitizing agent) and orlistat (an anti-obesity drug) aiming to achieve weight loss and hence higher ovulation rate for the group of obese PCOS patients. Keeping an eye on all these background facts, we designed this systematic review and metaanalysis to compare the effects of metformin and

Soumya Ranjan Panda is senior Resident, Department of Obstetrics and Gynecology, IMS, BHU, Varanasi, UP. Madhu Jain is a Professor and Head, Department of Obstetrics and Gynecology, IMS, BHU, Varanasi, UP. Shuchi Jain is an Assistant Professor, Department of Obstetrics and Gynecology, IMS, BHU, Varanasi, UP. Riden Saxena is a Phd Scholar, Department of Obstetrics and Gynecology, IMS, BHU, Varanasi, UP. Smrutismita Hota is a Junior Resident, Department of Radiodiagnosis, IMS, BHU, Varanasi, UP.

✉ Madhu Jain
drpanda83@gmail.com

[1] Department of Obstetrics and Gynecology, IMS, BHU, Varanasi, UP, India

[2] Department of Radiodiagnosis, IMS, BHU, Varanasi, UP, India

orlistat on various aspects of PCOS and to pick the better among the two drugs.

Materials and Methods This is a systemic review of randomized control trials that studied the effectiveness of orlistat versus metformin in terms of improvement in ovulation rate, weight loss, lipid profile, etc. Systematic literature search over the period January 2000–December 2016 was performed in the following electronic databases: Medline, embase, google scholar, pubmed and The Cochrane Library and only randomized controlled clinical trials were included in our study. All authors carefully went through all sources of information independently.

Results According to this study, weight loss, testosterone level after 4 weeks of treatment, total serum cholesterol and triglyceride level showed significant fall in orlistat-treated group.

Conclusion Our review shows that orlistat is a more effective drug than metformin and should be the preferred drug in obese PCOS in combination with weight loss.

Keywords Polycystic ovarian syndrome · Orlistat · Metformin · Obesity

Introduction

Polycystic ovarian syndrome (PCOS) is the most commonly prevalent endocrinopathy of reproductive age group women and is characterized by chronic anovulation and androgen excess with the predominant clinical manifestation being oligomenorrhea, hirsutism, and acne. The prevalence is as high as 15% when Rotterdam criteria are used for its diagnosis [1]. Increased insulin resistance (IR) is the central pathophysiologic mechanism responsible for increased risk of developing type 2 diabetes, the adverse cardiovascular risk as well as androgen excess and infertility in PCOS patients. Obesity which has been recently designated as an epidemic is often associated with PCOS. The prevalence was 40–60% among women with PCOS [2]. This makes 'weight loss' as the first-line treatment approach in overweight PCOS women [2].

These pathophysiological mechanisms have led to trials involving pharmacotherapy like metformin (an insulin-sensitizing agent) and orlistat (an anti-obesity drug) aiming to achieve weight loss and hence higher ovulation rate for the group of obese PCOS patients.

This is a systemic review of randomized control trials that studied the effectiveness of orlistat versus metformin in terms of improvement in ovulation rate, weight loss, lipid profile, etc.

Materials and Methods

Systematic literature search was performed in the following electronic databases: Medline, embase, google scholar, pubmed and The Cochrane Library. We performed a search over the period January 2000–December 2016 and only randomized controlled clinical trials (RCT) comparing the effects of orlistat and metformin were included. Search terms were as follows: "orlistat", "metformin", "polycystic ovary syndrome", "insulin resistance", etc. Six randomized control trials were eligible for our study. All authors carefully went through all sources of information independently. One review author extracted data from the included studies and the second author checked the extracted data. Information on the characteristics of a trial was extracted from each included trial. The characteristics of each study has been described in Table 1. All the statistical analysis was done using Statistical Software SPSS Version 20. Flow chart of the study selection is shown in Fig. 1.

Results

As shown in Table 2, the ovulation rate is higher for orlistat group in the studies done by Metwally et al. [3] (40 vs. 25%; p value − 0.10) and Kumar et al. [4] (33.3 vs. 23.3%; p value − 0.418). On the contrary, Ghandi et al. [5] have shown higher ovulation rate for metformin (15% for orlistat group vs. 30% for metformin group; p value − 0.108). But none of these studies have statistically significant results.

In view of Table 3, Jayagopal et al. [6] showed that the reduction in weight and after treatment with orlistat was more significant than seen in the metformin-treated group (4.69 vs. 1.02%, p value − 0.006). Similarly according to Kujawska-Łuczak et al. [7], the percentage change of weight loss and BMI was more in orlistat-treated group than that of metformin (-3.2 ± 0.8 vs. -1.7 ± 0.4; p value < 0.05 for weight loss and -4.9 ± 1.3 vs. -9.4 ± 2.3; p value < 0.05 for BMI). On comparison, the difference between the above said groups was found to be statistically significant for the concerned parameters. On the other hand, the studies by Metwally et al. [3], Kumar et al. [4], Ghandi et al. [5] and Cho et al. [8] could not found a statistically significant result between both arms as far as weight loss or BMI is concerned (p value 0.40, 1.000, > 0.05, 0.07 respectively for the above four studies).

Metwally et al. [3] have shown that there is a significant fall in testosterone level after 4 weeks of treatment with orlistat while for metformin this period appears to be 8 weeks, but without significant change in SHBG

Table 1 Characteristics of the included studies

References	Country	PCOS criteria	Types of studies	Dosage	Length (weeks)	Age (PCOS-orlistat group vs. Metformin group) Mean ± SD	N (PCOSorlistat/ metformin group)
Jayagopal et al. [6]	UK	NA	Prospective, randomized, open-label study	Orlistat: 120 mg three times per day; Metformin: 500 mg once daily for the first week, 500 mg twice daily for the next week and 500 mg three times daily for the remainder of the study period	12	27.0 ± 4.12 (all participants)	10/11
Metwally et al. [3]	UK	Rotterdam	Randomized controlled trial	Orlistat: 120 mg twice daily Metformin: initially as 500 mg once daily after meals for one a week followed by 500 mg twice daily for 4 weeks then increased in 500 mg increments every 4 weeks to a maximum of 2000 mg per day	12	30.6 (± 1.6) vs. 28.8 (± 0.9) [*p* value 0.34]	20/20
Cho et al. [8]	UK	Rotterdam	Randomized, open-label parallel study	Orlistat: 120 mg three times per day; Metformin: 500 mg once daily for the first week, 500 mg twice daily for the next week and 500 mg three times daily for the remainder of the study period	12	26.4 ± 6.7 (all participants)	10/10
Ghandi et al. [5]	Poland	Rotterdam	Randomized, open-label parallel study	Orlistat: 120 mg three times per day; Metformin: 500 mg once daily for the first week, 500 mg twice daily for the next week and 500 mg three times daily for the remainder of the study period	12	27.0 ± 44.0 (all participants)	40/40
Kumar et al. [4]	India	Rotterdam	Randomized controlled trial	Orlistat: 120 mg two times per day; Metformin was incremented stepwise to maximum 500 mg 3 times a day	12	NA	30/30
Kujawska-Łuczak et al. [7]	Iran	Rotterdam	Prospective randomized open-label study	Orlistat: 120 mg three times per day; Metformin: 500 mg twice daily	12	31.4 ± 8.2 years (all participants)	36/37

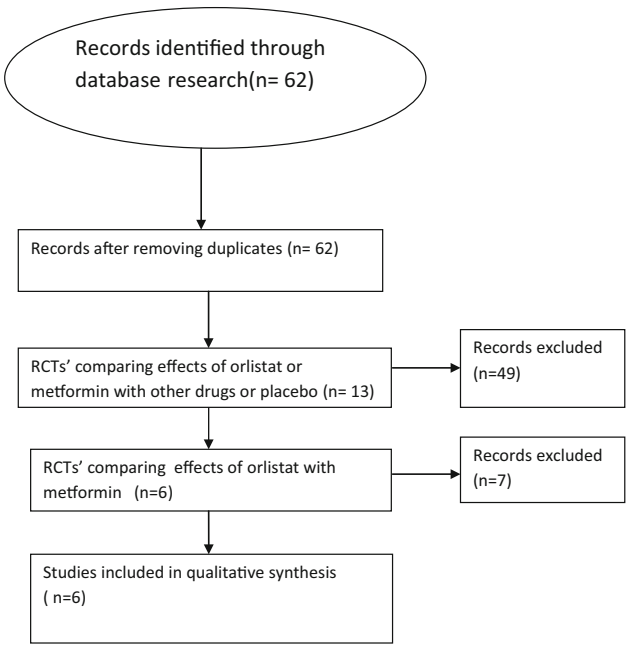

Fig. 1 Flow chart showing the selection of literatures that are included in our study

concentration in either group. According to Ghandi et al. [5], patients with orlistat have a significant fall in serum testosterone level after 12 week of treatment (percentage change from baseline serum testosterone level is − 19.37 ± 3.52 with p value < 0.001) while for those with metformin the fall in serum testosterone level was not statistically significant (percentage change from baseline −17.30 ± 5.30 with p value 0.053). Similarly, Cho et al. [8] have shown significant fall in free androgen index from baseline (− 22·9 ± 7.4; p value 0.017 for metformin arm vs. − 20.8 ± 5.8; p value 0.007 for orlistat arm) and significant increase in SHBG concentration from baseline (13.3 ± 3.1; p value < 0.05 for orlistat arm vs. 14.3 ± 5.0; p value < 0.05 for metformin arm) in both groups. While comparing the fall in testosterone level in orlistat-treated group with those treated with metformin, none of the concerned studies shows statistically significant result (Table 4).

As far as lipid profile is concerned (Table 5), Ghandi et al. [5] showed that treatment with orlistat resulted in a significant decline in total serum cholesterol and triglyceride on the contrary metformin treatment caused a

Table 2 Effect on ovulation rate (%)

Study group	Orlistat	Metformine	*p* value
Metwally et al. [3]	40	25	0.10
Kumar et al. [4]	33.3	23.3	0.418
Ghandi et al. [5]	15	30	0.108

Table 3 Effect on BMI and weight loss

Study group	Percentage change in BMI		Percentage change in wt loss	
	Orlistat	Metformine	Orlistat	Metformine
Jayagopal et al. [6]	NA	NA	4.69 ± 1.2	1.02 ± 0.9
p value			0.006	
Metwally et al. [3]	(−) 0.7	(−) 2	NA	NA
p value	0.40			
Ghandi et al. [5]	(−) 4.48 ± 0.47	(−) 4.55 ± 0.7	NA	NA
p value	> 0.05 (non significant)			
Kumar et al. [4]	− 8.12 ± 6.17	− 8.40 ± 0.65	NA	NA
p value	1.000			
Kujawska-Łuczak et al. [7]	− 3.2 ± 0.8	− 1.7 ± 0.4	− 9.4 ± 2.3	− 4.9 ± 1.3
p value	< 0.05		< 0.05	
Cho et al. [8]	(− 5.70) ± 0.80	(− 3.40) ± 1.00	NA	NA
p value	0.07			

Table 4 Effect on testosterone and SHBG levels

Study group	Change in testosterone levels (ng/dl) over 12 week		Change in SHBG levels (ng/dl) over 12 week	
	Orlistat	Metformine	Orlistat	Metformine
Jayagopal et al. [6]	− 16.8 + 7.1	− 14.69 + 9.6	+ 4.16 + 2.9	+ 1.46 + 4.0
p value	0.973		0.197	
Metwally et al. [3]	Sig fall after 4 weeks therapy	Sig fall after 8 weeks therapy	No significant change	No significant change
Ghandi et al. [5]	− 19.37 ± 3.52 (significant fall)	− 17.30 ± 5.30 (non significant fall)	NA	NA
	Non significant			
Kumar et al. [4]	(−) 17.68 + 4.18	(−) 12.89 + 3.12	4.67 + 7.83	13.2 + 33.78
p value	0.712		0.438	
Cho et al. [8]	NA	NA	13.3 ± 3.1 (significant increase)	14.3 ± 5.0 (significant increase)
p value			Non significant	

significant reduction in serum triglyceride only but not that of serum cholesterol. When the above result is compared between metformin and orlistat-treated groups, the more fall in total cholesterol level that was associated with orlistat treatment was found to be statistically significant (− 9.39 ± 2.43 vs. −1.54 ± 1.76 for orlistat and metformin arm, respectively; *p* value 0.023). Similarly, the more fall in total cholesterol level (− 9.51 + 1.56 vs. − 4.33 + 2.90; *p* value 0.037) and serum LDL level (− 5.66 + 2.07 vs. − 1.32 + 1.82; *p* value 0.04) that was associated with orlistat treatment group was also found to be statistically significant as compared with that of metformin arm in the study by Kumar et al. [4].

Cho et al. [8] showed a significant improvement in insulin resistance with orlistat treatment (*p* value 0.013) but not with metformin treatment (*p* value 0.17) as assessed by

Table 5 Effect on lipid profile over 12 weeks

Study group	Change in total cholesterol		Change in triglyceride		LDL		HDL	
	Orlistat	Metformine	Orlistat	Metformine	Orlistat	Metformine	Orlistat	Metformine
Jayagopal et al. [6]	− 1.68 ± 4.5	+ 3.23 ± 3.8	+ 0.23 ± 9.5	− 0.63 ± 8.4	− 5.97 ± 4.8	+ 2.75 ± 4.1	+ 7.49 ± 4.6	+ 4.33 ± 3.9
p value	0.557		0.654		0.282		0.468	
Ghandi et al. [5]	− 9.39 ± 2.43	− 1.54 ± 1.76	− 15.26 ± 4.93	− 19.97 ± 3.40	NA	NA	NA	NA
p value	0.023		Non significant					
Kumar et al. [4]	(−) 9.51 + 1.56	(−) 4.33 + 2.90	(−) 5.24 + 3.14	(−) 0.98 + 3.34	(−) 5.66 + 2.07	(−) 1.32 + 1.82	2.88 + 2.3	2.37 + 2.68
p value	0.037		0.391		0.004		0.796	

Table 6 Effect on insulin resistance

Study group	Change in FBS		Change in fasting insulin		HOMA-IR	
	Orlistat	Metformine	Orlistat	Metformine	Orlistat	Metformine
Jayagopal et al. [6]	(−) 2.15 + 1.0	(−) 0.99 + 1.3 mmol/l	(−) 12.5 + 5.8 mic IU/ml	(−) 7.39 + 8.2	(−) 10.8 + 6.0	(−) 7.19 + 8.4
p value	0.426		0.426		0.756	
Kumar et al. [4]	0.90 + 2.29	(−) 2.10 + 2.16	8.35 + 5.54	(−) 0.86 + 4.12	10.56 + 7.45	(−) 3.78 + 3.78
p value	0.178		0.28		0.301	
Kujawska-Łuczak et al. [7]	0.31 ± 1.06	0.09 ± 0.69	− 2.4 ± 3.6	− 2.5 ± 13.8	− 0.58 ± 0.96	− 0.38 ± 2.56
p value	Non significant		Non significant		Non significant	
Cho et al. [8]	NA	NA	NA	NA	− 19.7 ± 6.4 (significant fall)	− 16.1 ± 6.8 (non significant fall)
p value					Significant difference	

HOMA-IR. Similarly, the biological variability of HOMA-IR was reduced significantly only in the orlistat-treated group(*p* value 0.015). None of any other study groups showed significant improvement in any of the biochemical parameters for assessing insulin resistance as described in Table 6.

Discussion

Metformin is an oral biguanide antihyperglycemic drug which, besides being an insulin sensitizer, seems to have a significant impact on ovulation rates also. On the other hand, orlistat promotes weight loss by decreasing fat absorption from intenstine (about 30%) [9] by irreversibly inhibiting gastric and pancreatic carboxylester lipase. Because weight loss is related to improvement in ovarian function, orlistat seems to have a role in betterment in ovulation rate. This fact indicates that the association of improvement of ovulation rate with either drug seems to be indirectly through weight loss and neither drug seems to have any direct effect on ovulation induction.

As far as reduction in weight and BMI is concerned Jayagopal et al. [6], Cho et al. [8] and Kujawska-Łuczak et al. [7] have found orlistat to be more effective than metformin. Although the weight losing effects of metformin have also been described in various studies [10], the metformin therapy is not associated with a smooth course as gastrointenstinal side effects are a major barrier to patient compliance. In fact in various studies, almost all dropouts occurred only in the metformin arm. This fact suggests that orlistat may be a more preferable weight reducing agent due to better tolerability and compliance.

Obesity leading to decreased concentrations of SHBG is the prime cause for increased serum testosterone concentrations. Interestingly, we could not found any significant

Table 7 Summary of our systematic review

	Studies that favour Orlistat with significant difference	Studies that favour Metformin with significant difference
Ovulation rate	None	None
Percentage change in BMI	1. Kujawska-Łuczak et al. [7]	None
	2. Cho et al. [8]	
Percentage change in weight loss	1. Jayagopal et al. [6]	None
	2. Kujawska-Łuczak et al. [7]	
S. testosterone/free androgen index	None[a]	None
SHBG	None	None
LDL	1. Kumar et al. [4]	None
Total Cholesterol	1. Ghandi et al. [5]	None
	2. Kumar et al. [4]	
Triglyceride	None	None
HOMA-IR	1. Cho et al. [8]	None

[a]Although none of the studies shows a statistically significant results while comparing between the orlistat and the metformin arm, but some of the studies like Ghandi et al. [10] and Cho et al. [13] have found a statistically significant improvement from baseline values over the course of the treatment with orlistat only and not with metformin. Other studies like Metwally et al. [8] found a delayed effect of metformin in comparison to orlistat (8 vs. 4 weeks) to find a statistically significant improvement result from baseline values. These facts also favour the use of orlistat in PCOS in comparison to metformin

improvement in plasma concentrations of SHBG in any of the RCTs included in our study. So there must be other mechanisms that lead to decreased testosterone concentrations. The most logical explanation would be, moderate weight loss achieved by either metformin or orlistat, even though insufficient to improve serum SHBG concentrations, but may be sufficient enough to decrease serum testosterone levels via an attenuating effect on insulin like growth factor binding protein-I and thus inhibiting its stimulatory effect on P450c17α. (Thus decreased activity of P450c17α, leads to decreased levels of serum testosterone).

Although none of the RCTs showed any significant difference between effects of two drugs in terms of change in serum testosterone level, orlistat had its edge in preference to metformin as shown by Metwally et al. [3] and Ghandi et al. [5]. While orlistat showed an early effect (as early as 4 weeks) in the former study; metformin did not show any significant fall of serum testosterone level in the latter study. Also in another study, metformin reduced weight and waist circumference but did not affect testosterone level [11]. The delayed effect of metformin on androgen concentrations on some of the studies may indicate the need for a longer duration of therapy or may be a result of the initial low dose of metformin.

As shown by Ghandi et al. [5] and Kumar et al. [4] clearly orlistat has better effect than metformin in terms of improvement in lipid parameters.

Cho et al. [8] showed a significant improvement in insulin resistance in the orlistat-treated arm only and the difference was statistically significant as compared to metformin-treated arm. Neither of the other two RCTs included in our systematic review showed any improvement in insulin resistance by any of the drugs.

This could be explained due to the large variability in HOMA-IR values, which can be prevented in the future studies using a larger study sample.

On summarizing our systemic review results (Table 7), the list of various aspects of PCOS that are found to be improved with orlistat treatment and bearing a statistically significant difference with that of metformin are: percentage change in BMI, percentage change in weight loss, serum LDL level, serum total cholesterol level and insulin resistance in terms of HOMA-IR. Nevertheless, nausea and diarrhoea are the side effects of metformin which reduce patients compliance and suitability of its use.

On the basis of our systematic review, we can now recommend to prefer orlistat over metformin for use in cases of PCOS, especially in conjunction with exercise. However, at this stage we need to address some of the common adverse effects and drug interactions of orlistat which should be kept in mind while prescribing this drug.

Adverse Effects

Common side effects, those have been identified with the consumption of orlistat, include increased bowel

movement, oily stool, oily spotting and stomach pain [12]. But these gastrointenstinal adverse events generally resolve with ongoing orlistat treatment. Again as we have already discussed, treatment with metformin is also associated with similar gastrointenstinal side effects.

Some cases of serious liver injury have been reported since 1999. The US FDA review regarding the same identified a total of 13 cases of severe liver injury, between April 1999 and August 2009 out of an estimated 40 million people worldwide who had used orlistat. The U.S. FDA advised healthcare professionals to continue prescription of orlistat in August 2009, because severe liver injury was rare. Systemic adverse effects have rarely been reported with orlistat and, furthermore, many of the systemic adverse effects that have been associated with orlistat have not been reported in clinical trials, but in reports of weaker validity, such as case reports.

Contraindications

Chronic malabsorption syndrome or cholestasis is the contraindications for orlistat therapy.

Drug Interactions

Orlistat has been reported to interact with pharmacokinetics and pharmacodynamics of some drugs like fat-soluble vitamins, warfarin, amiodarone, ciclosporin, lamotrigine, valproic acid, vigabatrin, gabapentin, thyroxine [13]. To describe each and every interaction in detail is beyond the scope of this review. But here, we are highlighting some of the important interactions.

Interaction with Fat Soluble Vitamin

Orlistat is reported to cause decreased absorption of fat soluble vitamins. There is a significant reduction in absorption of betacarotene and vitamin E, but not vitamin A, in healthy volunteers with short-term use of orlistat [13]. In most of the studies although the plasma concentrations of fat soluble vitamins (A, D, E and betacarotene) decreased among subjects taking orlistat, but it remained within the clinical reference range during the entire study period [13].

To reduce the gastrointestinal events, orlistat should be taken with a low fat diet. Patients should be strongly encouraged to take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate Nutrition.

Interaction with Thyroxin

Thyroxine absorption is influenced by the content of the GI tract. Orlistat may bind to thyroxine and prevent its absorption from the small bowel. Clinicians should be aware of this potential interference of this drug with thyroxine absorption [13]. Levothyroxine and orlistat should be administered at least 4 h apart.

Interaction with Warfarin

Orlistat may reduce the absorption of fat-soluble vitamin K, thus resulting in a lowering of warfarin dose requirements. This is why patients on warfarin treatment should be closely monitored [13]. However, there is no conclusive evidence regarding the same.

At present, there is no guideline regarding the duration of use of orlistat for PCOS. However, based on the various randomized control trials that studied the various effects of orlistat, a treatment duration of minimum 3–6 month can be accepted as reasonable [3–8].

Limitations of the Study

Relatively less number of study population of the RCTs included in our systematic review constitute the only relative limitation of our study. However, after gathering a lot of fact in favour of orlistat this systematic review can safely recommend it over metformin for treatment of PCOS.

Conclusion

The analysis of these trials showed that both orlistat and metformin were associated with nonsignificant improvement, in many of the endocrine and metabolic parameters studied. However, the changes seen in terms of percentage change from baseline were more marked in the orlistat-treated group, perhaps suggesting that weight reduction had an overall stronger impact on these parameters than the insulin-sensitizing effect of metformin, the mechanism of which remains largely unknown. Based on the results of this systemic review of randomized control trials and also keeping an eye over the side effect profile of metformin, we recommend to prefer orlistat as a safe and effective therapy over metformin for treatment of polycystic ovarian syndrome preferably in combination with weight reduction. More research is recommended in this area.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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