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REVIEW ARTICLE

Metformin versus Orlistat for The Management of Infertile Obese Patients with polycystic Ovary Syndrome; A Randomized Controlled Trial

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ABSTRACT

Background: There is an increase in the prevalence of obesity-related reproductive disorders, particularly anovulation and infertility so , this indicates use of insulin sensitizing agents such as metformin and use of weight reduction agents such as orlistat in order to achieve reduction of BMI, reduce androgenic effect and improve ovulation . To the best of our knowledge, no studies in this respect was performed in Zagazig University before. Our study aimed to asses the effect of orlistat versus metformin on improvement of ovulation rate, weight loss and lipid and hormonal profile.

Methods: This randomized controlled trial was conducted at Zagazig University Hospital's outpatient clinic on 132 patients diagnosed with polycystic ovary syndrome. All cases were subjected to full history taking including, general examination and laboratory investigations including FSH, LH, TSH, free T4, free testosterone and prolactin level.

Results: There was no statistical significant difference between both groups as regard ovulation rate. There was significant changes between studied groups at 1st and **3rd** month as regard anthropometric data except BMI was insignificant at 1st month. Also, there was significant difference between studied groups as regard to laboratory data at 1st and 3rd month except FSH at 3rd month was insignificant.

Conclusions: We advise choosing metformin as a safe and effective treatment over orlistat for the treatment of polycystic ovarian syndrome, preferably in conjunction with weight loss and a healthy lifestyle.

Keywords: Metformin; Orlistat; PCO;Infertility

INTRODUCTION

According to various diagnostic criteria, PCOS (polycystic ovarian syndrome) affects 4% to 20% Among women who are of reproductive age, making it the most frequent endocrinopathy **[1].**

PCO, which accounts for up to 80% of one of the most common reasons of infertility is anovulatory infertility. Chronic anovulation and androgen excess are its defining features oligomenorrhea, acne, and hirsutism being the most common clinical manifestations.

Based on the Rotterdam criteria, the prevalence can reach up to 15% **[2]**.

The Rotterdam criterion explains that a PCOS diagnosis requires the presence of two of the three symptoms. These characteristics include anovulation, evidence of biochemical or clinical polycystic ovaries' morphological appearance on ultrasound scans, as well as hyperandrogenism **[3]**. When utilizing older Rotterdam transducers, PCO morphology by transvaginal ultrasonography is defined as an ovarian volume greater than 10 cm^ and/or more than 12 follicles measuring 2–9 mm. These transducers can be changed with 8 MHZ transducers, which can measure more than 20 follicles measuring 2–9 mm **[4].**

Infertility, hirsutism, and irregular menstruation are more prevalent in obese PCOS women. Eighty-five to eighty-five percent obesity is characterized as having a

woman's body mass index (BMI) if it is 25 or higher with PCOS. Fatality is anticipated to worsen several of the fundamental biochemical aspects of PCO that are critical in its pathogenesis **[5].**

Insulin resistance (IR), diabetes, dyslipidemia, hypertension, and hyperinsulinemia are all linked to PCOS. The primary pathophysiologic mechanism behind elevated insulin resistance (IR), unfavorable cardiovascular risk, androgen excess, as well as infertility ndividuals with PCOS are more likely to develop type 2 diabetes **[6].**

Recent designations of obesity as an epidemic are frequently linked to PICS. The proportion of PCOS-affected women who had it was 80–85%. For overweight PCOS women, this means that "weight loss" is the recommended initial course of treatment. Due to these pathophysiological pathways, trials using pharmacotherapy, such as the insulin-sensitizing agent metformin and the anti-obesity medication orlistat, have been conducted with the goal of helping the obese PCOS patients lose weight and increase their ovulation rate **[7].**

Metformin is a Antihyperglycemic drug biguanide It has demonstrated advantages PCOS individuals with hyperandrogenism, hyperinsulinemia, and menstrual cyclicity, whether they are obese or not. This is probably because the drug is helping with both abdominal obesity and insulin clearance **[8].**

Elevated circulation insulin and insulin-like growth factor-1 (IGF-1) levels lead to ovarian theca cells to overproduce androgens in women with PCOS. Metformin prevents theca cells from producing androgens, partly via lowering LH output from the pituitary, which triggers ovulation and regular menstrual cycles. In obese and non-obese PCOS patients, metformin is clinically useful for ovulation induction, menstrual cycle management, and pregnancy **[9].**

Lipstickin, a strong Saturated derivative of orlistat, It is a naturally occurring lipase inhibitor that was discovered in the microorganisms Streptomyces toxytricini. Orlistat, however, was chosen for development as an anti-obesity medication over lipstatin medication due to its greater simplicity and stability **[10].**

One medication used to treat obesity is called orlistat. The intestine's natural triglyceride-breaking enzymes, pancreatic and stomach carboxylester lipase, are effectively and irreversibly inhibited by it. Dietary triglycerides are not broken down into absorbable free fatty acids if lipase activity is inhibited; instead, they are ejected undigested. The primary effect of orlistat upon oral administration is local lipase inhibition in the GI tract; only trace amounts are absorbed systemically. The feces are the main method of excretion. Orlistat helps people lose weight by roughly 30% reducing the amount of fat absorbed from the intestinal lumen. **[11, 12].**

METHODS

In this controlled, randomised study, 132 females suffering from polycystic ovary syndrome were treated at the outpatient clinic of Zagazig University Hospital during the period from January 2023 to June 2023. Every participant received an explanation of the study's goal and their Consent was gained with knowledge. Informed written consent was obtained from all participants. The study was approved by Zagazig University's Faculty of Medicine's ethical committee (IRB#10278).

Inclusion criteria: Patients with polycystic ovary on imaging (i.e. > 12 follicles in each ovary measuring 2-9 mm in diameter or an ovarian volume > 10 mL) with Rotterdam criteria of PCO diagnosis, age < 37 years and patients with body Mass index (BMI) > 30 were included in the study.

Exclusion criteria : Individuals with renal or hepatic impairment, malabsorbtion syndrome, cholestasis, or diabetes who should not be using any of the drugs (type 2 or type 1) and pregnancy (excluded by pregnancy test in women with amenorrhea or oligomenorrhaea) were excluded from the study.

Every case had a thorough history taken, along with a general examination and lab tests usually include FSH, LH, TSH, free T4, free testosterone and prolactin level.

A computer-generated randomization was used for the purpose of carrying out the randomization. The statistician constructed a

set of identical, numbered in sequence, sealed envelopes that were used for the allocation concealment process. These envelopes were stored with the research nurse.

There was a random selection made to divide all of the patients who meet the inclusion criteria between the groups, each group includes 44 cases. Metformin was administered to the individuals in group (A), and orlistat was given to the individuals in group (B). They begun taking the medication as 500 mg once daily after meals for the first week in order to reduce the risk of gastrointestinal distress. After that, they took 500 mg twice daily for the next two weeks. After thereafter, the dose was increased by 500 mg per week, all the way up to a maximum of 2000 mg per day throughout the remainder of the time that the trial was being conducted. Additionally, women on metformin were provided with general dietary counseling. And emphasized the importance of consistent physical activity. Orlistat was provided at a regular dose of 120 mg twice day for those in group (B) of the study. To prevent steatorrhea, it was recommended that women using orlistat begin a low-fat diet that contains less than 5% fat (consisting primarily of plant foods like vegetables, fruits, and whole grains, with a modest quantity (150-200gm) of foods derived from animals, such as lean meat and low-fat dairy). The control group, designated as Group (C), received placebo in addition to required to participate in an activity and nutrition regimen .

Follow up:

Over the course of three months, the following was noted at four-week intervals: The patient's medical history includes information on altered menstrual cycles, androgenic symptoms such as acne and hirsutism, medication adherence, occurrence of side effects, major adverse effects, adherence to the diet, physical activity, and physical examination. variation in BMI.

Study end-point:

The attainment of ovulation, the conclusion of the three-month course of treatment, or a reduction in body mass index to less than 30 were the clinical end goals.

Measurements of outcomes:

Primary outcomes: Occurrence of ovulation diagnosed by us (folliculometry), visit was at day 11 for folliculometry and endometrial measurement. At least two of the following ultrasonography parameters—a. a decrease in follicular diameter, b. a blurring of the follicular border, and c. the presence of fluid in the cul-de-sac—were used to confirm ovulation.

Secondary outcomes: variations in the BMI and waist circumference, the hormonal profile, which includes the menstrual pattern and the improvement or degradation of androgenic traits (hirsutism and acne).

STATISTICAL ANALYSIS

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0**. (**Armonk, NY: IBM Corp**)** Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Chi-square test, student t-test and ANOVA test were used. Significance of the obtained results was judged at the 5% level.

RESULTS

Studied groups were matched as regard to age, education, residency, waist, weight, BMI, irregular periods and androgenic symptoms (Table 1).

The studied groups are matched as regard baseline LH, Testosterone, FSH or TSH (Table 2).

There was no statistical significant difference between both groups as regard ovulation rate (Table 3).

There was a significant difference between baseline anthropometric data and follow up anthropometric data (1 month and 3 months) in group A and B and there was a significant difference between baseline anthropometric data and follow up anthropometric data (1 month and 3 months) except BMI was insignificant in group C (Table 4).

We found a significant changes between studied groups at 1st and **3rd** month as regard

anthropometric data except BMI was insignificant at 1st month (Table 5).

We found difference between studied groups as regard changes of anthropometric data was significant (Table 6).

Patients in group A had significant changes in laboratory data from baseline to 3rd month except FSH were insignificant. Patients in group B had significant changes in laboratory data from baseline to 3rd month except LH and TSH were insignificant. Patients in group C had significant changes in laboratory data from baseline to 3rd month except FSH were insignificant (Table 7).

There was significant difference between studied groups as regard to laboratory data at 1st and 3rd month except FSH at 3rd month was insignificant (Table S1).

There were significant differences between studied groups as regard to changes of laboratory data (Table S2).

There was no significant difference between the studied groups as regard irregular periods and androgenic symptoms at 3rd months (Table S3).

There was no significant difference between the studied groups as regard irregular periods and androgenic symptoms changes from baseline to 3rd month (Table S4).

Table 1: Comparison between studied groups as regard baseline data

	Group A (Metformin) N=44		**Group B (Orlistat) N=44**		**Group C (Control) N=44**		**P value**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Age (years)	28.9	1.9	28.3	2.7	28.2	2.5	.38
	N	**%**	**N**	**%**	**N**	**%**	
Waist	113.3	9.6	117.7	8.6	114.9	10.1	.09
Weight	98.3	1.5	98.3	1.3	97.9	1.5	.46
BMI	35.2	3.6	36.5	3.6	35.7	3.7	.26
Irregular cycles							
Yes	42 (95.45%)		44 (100%)		42(95.45%)		.88
No	2 (4.55%)		0		2 (4.55%)		
Androgenic symptoms							
Yes	22 (50%)		20 (45.45%)		20 (45.45%)		.55
No	22 (50%)		24 (54.55%)		24 (54.55%)		

- Group A : metformin group including 44 cases
- Group B : orlistat group including 44 cases
- Group C : control group including 44 cases

Table 2: Baseline Laboratory finding in the three groups

	Group A (Metformin) N=44		**Group B (Orlistat) N=44**		**Group C (Control) N=44**		**P Value**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
LH (mIU/ml)	7.8	4.0	6.7	4.5	6.6	3.8	0.25
Testosterone (nmol/liter)	4.2	0.4	4.1	0.6	4.1	0.3	0.45
FSH (mIU/ml)	4.3	1.2	3.8	2.1	4.0	1.2	0.27
TSH (mIU/L)	3.3	1.5	3.7	0.02	3.5	1.5	0.39

Table 3: Comparison between studied groups as regard ovulation rate at the end of the 3rd month

	Group A (Metformin) N=44		**Group B (Orlistat) N=44**		**Group C (Control) N=44**		**P Value**
	N	**%**	**N**	**%**	**N**	**%**	
Ovulation rate	13	29.5	8	18.2	6	13.6	0.127

Chi Square, p value >0.05: nonsignificant

Table 4: Comparison between baseline and follow up of anthropometric data in group A, B and C.

	Baseline		1 month		3 months		Change		P Value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
In group A									
Waist	113.3	9.6	108.5	7.5	104.5	5.3	-9	10	**0.001***
Weight	98.3	1.5	95.2	1.2	91.3	0.8	-7	2	**0.001***
BMI	35.2	3.6	34.1	3.1	31.2	2.2	-3.9	4.0	**0.001***
In group B									
Waist	117.7	8.6	110.1	7.4	105.4	6.4	-12.3	11.0	**0.001***
Weight	98.3	1.3	95.1	1.1	90.9	0.8	-7.4	1.7	**0.001***
BMI	36.5	3.6	33.4	3.2	30.9	3.1	-5.6	4.3	**0.001***
In group C									
Waist	114.9	10.1	110.4	5.3	107.1	4.6	-7.8	9.9	**0.001***
Weight	97.9	1.5	95	1.1	92.6	0.7	-5.3	1.7	**0.001***
BMI	35.7	3.7	33.4	2.1	32.8	3.1	-2.9	4.0	0.3

ANOVA test, p value <0.05 significant

Table 5: Comparison between studied groups as regard anthropometric data at 1st and 3rd month

	Group A (Metformin) N=44		Group B (Orlistat) N=44		Group C (Control) N=44		P Value
	Mean	SD	Mean	SD	Mean	SD	
Anthropometric data at 1st month							
Waist	108.5	7.5	110.1	7.4	110.4	5.3	**0.001***
Weight	95.2	1.2	95.1	1.1	95	1.1	**0.001***
BMI	34.1	3.1	33.4	3.2	33.4	2.1	0.18
Anthropometric data at 3rd month							
Waist	104.5	5.3	104.5	6.4	104.5	4.6	**0.001***
Weight	91.3	0.8	90.9	0.8	92.6	0.7	**0.001***
BMI	31.2	2.2	30.9	3.1	32.8	3.1	**0.001***

ANOVA test, p value <0.05 significant

Table 62: Comparison between studied groups as regard changes of anthropometric data at the end of the study .

	Group A (Metformin) N=44		Group B (Orlistat) N=44		Group C (Control) N=44		P Value
	Mean	SD	Mean	SD	Mean	SD	
Change BMI	-3.9	4.0	-5.6	4.3	-2.9	9.9	**0.01***
Change Waist	-9	10	-12.2	11.0	-7.8	1.7	**0.012***
Change weight	-7	2	-7.3	1.7	-5.3	4	**0.001***

ANOVA test, p value <0.05 significant .

Table 73: Comparison between baseline and follow up of Laboratory data in the studied groups

	Baseline		1 month		3 months		P Value
	Mean	SD	Mean	SD	Mean	SD	
In group A							
LH (mIU/ml)	7.8	4.0	6.2	2.9	5.5	2.1	**0.04***
Testosterone (nmol/liter)	4.2	0.4	3.3	0.4	3.0	0.0	**0.042***

FSH (mIU/ml)	4.3	1.2	3.5	0.9	2.3	0.9	0.38
TSH (mIU/L)	3.3	1.5	3.4	1.3	2.7	0.7	**0.018***
In group B							
LH (mIU/ml)	6.7	4.5	5.6	3.9	5.4	2.9	0.16
Testosterone (nmol/liter)	4.1	0.6	3.3	0.7	3.0	0.0	**0.02***
FSH (mIU/ml)	3.8	2.1	2.3	1.5	3.0	1.4	**0.013***
TSH (mIU/L)	3.7	0.02	3.4	0.02	2.8	0.02	0.1
In group C							
LH (mIU/ml)	6.6	3.8	7.6	3.8	6.3	3.6	0.17
Testosterone (nmol/liter)	4.1	0.3	3.1	0.3	3.91	0.2	**0.001***
FSH (mIU/ml)	4	1.2	3	1.2	3	1.1	0.27
TSH (mIU/L)	3.5	1.5	4.5	1.5	3.4	1.3	**0.001***

ANOVA test, p value <0.05 significant

DISCUSSION

In the current study, regarding ovulation rate in this study there were no substantial variation in ovulation rate among all groups. Ovulation rate was 29.5% in the 1st group compared to 18.2% in the 2nd group and 13.6% in 3rd group This difference had no statistical significance (p=0.127).

Two studies have assessed ovulation rates, with similar statistical result , **Ghandi et al. [13]** examined ovulation rates solely following (and not prior to) the metformin or orlistat intervention; nevertheless, no variations were noted across the groups. **Kumar et al. [14]** also measured ovulation rates following the intervention and discovered that there were no differences in ovulation rates between orlistat and metformin users, but that ovulation rates were improved in the orlistat and metformin groups when compared with the control group.

As shown in **Panda et al. [15]** systematic review**,** similar to our study , **Ghandi et al. [13]** have demonstrated that the metformin group has a greater ovulation rate (15% compared to 30% for the orlistat group); *p* value − 0.108),

Conversely, in the research conducted by, the ovulation rate is greater for the orlistat group **Metwally et al. [16]** (40 vs. 25%; *p* value − 0.10) and **Kumar et al. [14]** (33.3 vs. 23.3%; *p* value − 0.418). However, the results of any of these research are not statistically significant.

Regarding androgenic symptoms and menstrual irregularity, all 3 groups shows variable degrees of improvement, which was more prominent in metformin group.

At the end of the study, 35% of patients in the metformin group and 25% of patients in the orlistat group reported improvements in their menstrual cyclicity. However, there was no statistically significant difference between the two arms in terms of the number of articipants who reported improvements at any of the follow-up visits.

The percentage of cases complain of androgenic symptoms decreased reaching 35% for the metformin group, 40% for the orlistat group, and 41% for the control group by the conclusion of the research. The percentage of participants reporting improvement of these symptoms at follow-up visits did not differ significantly across all groups.

Regarding anthropometric parameters , According to this study, there were notable differences in three groups' BMI, weight, waist circumference, and age.

When comparing the baseline and study end anthropometric characteristics, the orlistat group showed a greater improvement. Group A also had a change in the mean BMI (-3.9), Waist circumference (-13) and Weight (-7), in group B change in the mean of BMI (5.6), Waist circumference (17.2) and Weight (-7.3) , in group C change in the mean of BMI (2.9), Waist circumference (10.7) and Weight (5.3) .

Ovulation disorders are the primary cause of infertility in women with PCOS; obesity is another factor contributing to poor fertility that is linked to menstrual irregularities, excess androgen, hyperglycemia, insulin resistance, and dyslipidemia. BMI, waist-to-hip ratio (WHR), body weight, and waist

circumference are common indicators of body fat percentage. WHR is a crucial criterion to assess central obesity, but BMI is a widely used, trustworthy scientific indicator **[17].**

Vrbikova et al. [18] shown that losing weight can help obese PCOS women ovulate more frequently, have better menstrual cycles, and have successful pregnancies.

Similar to our study , In **Panda et al. [15]** systematic review, **Jayagopal et al. [19]** demonstrated that the weight loss following orlistat medication was greater than that observed in the group receiving metformin (4.69 vs. 1.02%, *p* value − 0.006).

According to **Kujawska-Łuczak et al. [20],** Compared to the metformin group, the orlistat-treated group had a greater percentage change in weight reduction and BMI (-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). Comparative analysis revealed that, for the relevant parameters, there was a statistically significant difference between the aforementioned groups.

A meta-analysis performed by **Wang et al. [21]** of pharmaceutical treatments to cause weight loss in overweight or obese PCOS women included 23 clinical studies, 941 participants, and examined the efficacy of orlistat, metformin, inositol, and liraglutide. Subgroup analysis revealed that after 12 weeks of treatment, only orlistat significantly lowered participants' BMI; waist circumference did not change.

In a prospective study by **Panidis et al. [22]** including 101 obese PCOS patients (BMI 34.5 ± 5.9 kg/m^2) and 29 obese Every participant, including women with regular menstrual cycles, received a low-calorie diet and engaged in appropriate-intensity exercise. Body weight, BMI, and WHR were all significantly lower in the PCOS and control groups after 6 months of orlistat medication; however, there was no discernible difference in the rates of BMI and WHR drop between the groups.

In a systematic review **by Graff et al. [23]**, For overweight/obese women with PCOS, all trials showing significant decreases in BMI and/or weight with orlistat (34–42). After orlistat treatment, women with PCOS had significant reductions in their waist or waist-to-hip ratio in five out of the six trials that assessed waist circumference. Furthermore, two trials contrasting the effects of metformin and orlistat revealed that both medications decreased PCOS women's waist circumference in an equivalent manner.

On the other hand, the studies by **Metwally et al. [16], Kumar et al. [14], Ghandi et al. [13]** and **Cho et al. [24]** did not find a statistically significant difference in BMI or weight reduction between the two arms (*p* value 0.40, 1.000, > 0.05, 0.07 respectively for the above four studies)..

According to this study, there was no discernible difference in the baseline levels of LH, testosterone, FSH, or TSH between the two groups. There was a statistically significant difference between the three groups at the conclusion of the trial. This study demonstrated that in group A, there were high significant difference between baseline LH and free testosterone and follow up LH and free testosterone (1 month and 3 months). In group B, there were significant difference between baseline Testosterone and follow up Testosterone (1 month and 3 months), but no significant difference between baseline LH and follow up LH). In group C, there were significant difference between baseline Free testosterone and follow up free testosterone (1 month and 3 months), but no significant difference between baseline LH and follow up LH. Improvement of hormonal profile mainly Free testosterone level was more prominent in metformin group .

Similarly, **Cho et al. [24]** have shown significant fall in free androgen index from baseline ($-22{\cdot}9 \pm 7.4$; *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 pairings. When comparing the decrease in testosterone levels between the metformin-treated and orlistat-treated groups,

no study that addresses the issue finds statistically significant results.

In a study by **Abdulaty et al. [25],** They demonstrated a substantial difference in LH post-treatment, free testosterone LH pre- and post-treatment, LH/FSH ratio, midluteal progesterone, and anti-mullerian hormone between the two groups.

Our finding is consistent with previous studies by **Velazquez et al. [26] and Nestler et al. [27]** wherein the serum level of LH is decreased by metformin medication. In their investigation, orlistat therapy did not considerably lower LH levels. Losing weight has been shown to lower serum LH levels and improve hyperinsulinemia in PCOS patients.

At various stages of insulin physiology, metformin and the other insulin-sensitizing medications interact. Given that these medications function through distinct pathways, it has been proposed that orlistat acts indirectly by causing weight loss, whilst the lowering of insulin may occur directly or indirectly through the pituitary LH synthesis and discharge. It appears that lengthier orlistat treatment is required to get a discernible drop in serum LH levels **[13].**

On the other hand, Song et al. [28] noted substantial drops in total testosterone and serum LH levels in every group, but no discernible variations between them. The levels of FSH did not significantly alter.

According to **Ghandi et al. [13]**, After 12 weeks of medication, the blood testosterone levels of orlistat patients significantly decrease (change from baseline in percentage terms) is -19.37 ± 3.52 with p value < 0.001) However, the decrease in serum testosterone levels (% change from baseline) was not statistically significant for individuals using metformin-17.30 ± 5.30 with p value 0.053).also, revealed that metformin treatment also decreased total testosterone and total cholesterol levels, however the drops were not statistically significant.

In a systematic review **by Graff et al. [23]**, In seven out of eight trials, taking orlistat was associated with a drop in testosterone levels.

The main factor contributing to elevated serum testosterone concentrations is obesity, which lowers SHBG concentrations. Interestingly, none of the RCTs included in the analysis showed a discernible increase in SHBG plasma concentrations **Panda et al. [15]** research. Therefore, lower testosterone concentrations must be caused by other causes. The most likely explanation is that, although metformin or orlistat did not significantly increase serum SHBG concentrations, their moderate weight loss may have been sufficient to lower serum testosterone levels by attenuating the stimulatory effect of insulin on growth factor binding protein-I on P450c17α. (Thus decreased activity of P450c17α, leads to decreased levels of serum testosterone) **[15].**

CONCLUSIONS

The examination of these studies revealed that ovulation rates were not significantly improved by either orlistat or metformin, at end of study there was significant difference between study groups in endocrine and metabolic parameters studied, with significant reduction of LH and free testosterone level in metformin group . However, changes in anthropometric parameter was more prominent in orlistat group. Based on the results of this, we advise choosing metformin as a safe and effective treatment over orlistat for the treatment of polycystic ovarian syndrome, preferably in conjunction with weight loss and a healthy lifestyle, but also keeping an eye on trials and the adverse effect profile and higher cost of orlistat. It is advised that this field sees more investigation.

REFERENCES

1. **Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R.** Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab. 2018; 83(9):3078–82.
2. **Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al.** Amsterdam ESHRE/ASRM Sponsored 3rd PCOS Consensus Workshop Group. Consensus on women's health aspects of polycystic ovary syndrome (PCOS). Hum Reprod. 2012; 27:14–24.
3. **Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group.** Revised 2013

Consensus on Diagnostic Criteria and Long-Term Health Risks Related to Polycystic Ovary Syndrome (PCOS).” *Hum. Reprod.*2014; 19 (1): 41–47.

4. **Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al.** Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum. Reprod. 2018; 33(9): 1602-18.
5. **Taylor AE.** Polycystic ovary syndrome. Endocrinol Metab Clin North Am. 2015; 27(4):877–902.
6. **Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al**. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab. 2016; 91(11):4237–45.
7. **Calcaterra V, Verduci E, Cena H, Magenes C, Todisco F, Tenuta E, et al.** Polycystic ovary syndrome in insulin-resistant adolescents with obesity: the role of nutrition therapy and food supplements as a strategy to protect fertility. Nutrients 2021; 13(6):1848.
8. **Kumari AS, Haq A, Jayasundaram R, Abdel-Wareth LO, Al Haija SA, Alvares M.** Metformin monotherapy in lean women with polycystic ovary syndrome. Reprod Biomed Online 2015; 10(1):100–4.
9. **Al-Deresawi S, Al-Rekaabi R, Edee A.** Evaluation of hormonal profile and insulin growth factor-1 gene expression before and after metformin treatment in women with polycystic ovary syndrome. Drug Invent. Today 2019; 12(11).
10. **Pommier A, Pons M, Kocienski** P. The first total synthesis of lipstatin. J Org Chem 2015; 60(22):7334–9.
11. **Dixon JB.** Weight loss medications--where do they fit in? Aust Fam Physician 2016; 35(8):576–9.
12. **Liu T, Liu T, Chen X, Shi Y.** Lipase inhibitors for obesity: A review. Biomed. Pharmacother 2020; 128: 110314.
13. **Ghandi S, Aflatoonian A, Tabibnejad N, Moghaddam HS.** The effects of metformin or orlistat on obese women with polycystic ovary syndrome: a prospective randomized open-label study. *J Assist Reprod Genet* 2011;28:591–6.
14. **Kumar P, Arora S.** Orlistat in polycystic ovarian syndrome reduces weight with improvement in lipid profile and pregnancy rates. *J Hum Reprod Sci.* 2014;7(4):255–61.
15. **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; Oct;68(5):336-43.
16. **Metwally M, Amer S, Li TC, Ledger WL.** An RCT of metformin versus orlistat for the management of obese anovulatory women. *Hum Reprod* 2009;24:966–75.
17. **Jiang Q, Shi Y.** Effect of orlistat on obese women with polycystic ovary syndrome. *J. bio-X res.* 2018; *1*(03):128-31.
18. **Vrbikova J, Hainer V.** Obesity and polycystic ovary syndrome. *Obes Facts* 2009; 2:26–35.
19. **Jayagopal V, Kilpatrick ES, Holding S, Jennings PE, Atkin SL.** Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. *J Clin Endocrinolmetab* 2015;90:729–33.
20. **Kujawska-Łuczak M, Musialik K, Szulińska M, Swora-Cwynar E, Kargulewicz A, Grzymisławska M, et al.** The effect of orlistat versus metformin on body composition and insulin resistance in obese premenopausal women: 3-month randomized prospective open-label study. *Arch Med Sci. 2017;* 13(4: 725-31.
21. **Wang FF, Wu Y, Zhu YH, Ding T, Batterham RL, Qu F, et al.** Pharmacologic therapy to induce weight loss in women who have obesity/overweight with polycystic ovary syndrome: a systematic review and network meta-analysis. *Obes Rev* 2018; 19:1424–45.
22. **Panidis D, Tziomalos K, Papadakis E, Chatzis P, Kandaraki EA, Tsourdi EA, et al.** The role of orlistat combined with lifestyle changes in the management of overweight and obese patients with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2014; 80:432–38.
23. **Graff SK, Mario FM, Ziegelmann P, Spritzer PM.** Effects of orlistat vs. metformin on weight loss- related clinical variables in women with PCOS: systematic review and meta- analysis. *Int. J. Clin. Pract.* 2016; *70*(6): 450-61.
24. **Cho LW, Kilpatrick ES, Keevil BG, Coady AM, Atkin SL.** Effect of metformin, orlistat and pioglitazone treatment on mean insulin resistance and its biological variability in polycystic ovary syndrome. *Clin Endocrinol.* 2009;70:233–37.
25. **Abdulaty Abdulaty Al-Qahwajy M, Khalil Ahmed Eissa A, Soliman Taha W, Ahmed Abdelmoaty M.** QRLISTAT (THE LIPASE INHIBITOR) THERAPY IN OVERWEIGHT AND OBESE SUB-FERTILE WOMEN. *AIMJ* 2022; *51*(2): 927-38.

26. **Velazquez EM, Acosta A, Mendoza SG.** Menstrual cyclicity after metformin therapy in polycystic ovary syndrome. *Obstet Gynecol* 2009;90:392–95.
27. **Nestler JE, Stovall D, Akhter N, Iuorno MJ, Jacubwicz DJ.** Strategies for the use of insulin-sensitizing drugs to treat infertility in women with polycystic ovary syndrome. *Fertil Steril.* 2012;77 :209–15.
28. **Song J, Ruan X, Gu M, Wang L, Wang H, Mueck AO.** *Effect of orlistat or metformin in overweight and obese polycystic ovary syndrome patients with insulin resistance. J. Gynaecol. Endocrinol.2017; 34(5): 413–17.*

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SUPPLEMENTARY MATERIAL

Table (S1) 4: Comparison between studied groups as regard 1st and 3rd month laboratory data

	Group A (Metformin) N=44		Group B (Orlistat) N=44		Group C (Control) N=44		P Value
	Mean	SD	Mean	SD	Mean	SD	
1st month laboratory data							
LH (mIU/ml)	6.2	2.9	5.6	3.9	7.6	3.8	**0.017***
Testosterone (nmol/liter)	3.3	0.4	3.3	0.7	3.1	0.3	**0.027***
FSH (mIU/ml)	3.5	0.9	2.3	1.5	3.0	1.2	**0.004***
TSH (mIU/L)	3.4	1.3	3.4	0.02	4.5	1.5	**0.001***
3rd month laboratory data							
LH (mIU/ml)	5.5	2.1	5.4	2.9	6.3	3.6	**0.001***
Testosterone (nmol/liter)	3.0	0.0	3.0	0.0	3.91	0.2	**0.001***
FSH (mIU/ml)	2.3	0.9	3.0	1.4	3.0	1.1	0.27
TSH (mIU/L)	2.7	0.7	2.8	0.02	3.4	1.3	**0.001***

ANOVA test, p value <0.05 significant

Table (S2): Comparison between studied groups as regard changes of laboratory data

	Group A (Metformin) N=44		Group B (Orlistat) N=44		Group C (Control) N=44		P Value
	Mean	SD	Mean	SD	Mean	SD	
Change LH	-2.3	4.6	-1.3	3.7	-0.3	3.7	**0.05***
Change Testosterone	-1.2	0.4	-1.1	0.4	-0.16	0.4	**0.001***
Change FSH	-2	1.4	-0.8	1.7	-1	1.4	**0.004***
Change TSH	-0.5	1.6	-0.9	1.6	0.11	1.6	**0.018***

ANOVA test, p value <0.05 significant

Table (S3): Comparison between studied groups as regard irregular periods and androgenic symptoms at 3rd month

	Group A (Metformin) N=44	Group B (Orlistat) N=44	Group C (Control) N=44	P value
Irregular periods				
Yes	29 (65.9%)	33 (75%)	35(79.5%)	0.1
No	15 (34.1%)	11 (25%)	9 (10.0%)	
Androgenic symptoms				
Yes	15(34.1%)	18 (40.9%)	18 (40.9%)	0.3
No	29 (65.9%)	26 (59.9%)	26 (59.9%)	

X^2: Chi Square

Table (S4): Comparison between studied groups as regard irregular periods and androgenic symptoms changes

	Group A (Metformin) N=44	**Group B (Orlistat) N=44**	**Group C (Control) N=44**	**P value**
Irregular periods				
Baseline	42 (95.45%)	44 (100%)	42(95.45%)	0.73
at 3rd month	29 (65.9%)	33 (75%)	35(79.5%)	
Androgenic symptoms				
Baseline	22 (50%)	20 (45.45%)	20 (45.45%)	
at 3rd month	15(34.1%)	18 (40.9%)	18 (40.9%)	0.45

X^2: Chi Square