Metformin and Orlistat for The Management of Infertile Obese Patients with polycystic Ovary Syndrome: Review Article

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disease in women of reproductive age. PCOS is characterized by ovulatory disruption, which can lead to infertility. Patients with PCOS are also more likely to have poor pregnancy outcomes. For obese women, lifestyle interventions are recommended first, which have general health benefits. For women who have difficulty changing their lifestyle, drugs for the treatment of obesity or bariatric surgery could be considered. Clomiphene citrate is the first-line medication after weight loss that has been utilized in the past. Letrozole is supplanting clomiphene as the best option for ovulation induction for now, particularly in patients with PCOS. Metformin can improve ovulation and pregnancy rates; however, it has minimal effects in terms of raising live birth rates. Second-line therapies include gonadotropins and laparoscopic ovary drilling. In vitro fertilization can be utilized as a third-line treatment for patients with PCOS who have failed ovulation induction therapy or have other infertility factors. In summary, to achieve fertility, patients with PCOS require standardized individualized therapy.

KeyWords: Metformin, Orlistat, PCO.

DOINUMBER:10.48047/NQ.2022.20.19.NQ99439 **NEUROQUANTOLOGY2022;20(19):4771-4779**

Introduction.

Metformin, FDA-approved in 1994, is an antidiabetic agent used in type 2 diabetes mellitus. Metformin comes in both immediate-release and extended-release and is available in several combination products with other antidiabetic agents (**1).**

Metformin is a biguanide drug that reduces blood glucose levels by decreasing glucose production in the liver, decreasing intestinal absorption, and increasing insulin sensitivity. Metformin decreases both basal and postprandial blood glucose levels. In PCOS, Metformin decreases insulin levels, which then decreases luteinizing hormone and androgen levels. Thus acting to normalize the menstruation cycle. It is important to advise premenopausal women of the increased potential for pregnancy when taking metformin (**2).**

In gestational diabetes, metformin is recommended as an alternative to insulin. Hyperglycemia is associated with congenital malformations. Therefore, metformin works to decrease blood glucose during pregnancy. Per Facts and Comparisons, metformin was in the class B pregnancy category under the old FDA system. It crosses the placenta and is present in breast milk (**3).**

Metformin is considered weight neutral with the potential for modest weight loss. It is also unlikely to cause hypoglycemia and may be potentially cardioprotective. The onset of metformin is about 3 hours after taking the medication with a half-life of 20 hours. Metformin is not metabolized in the liver, nor

does it have substantial protein binding. Metformin is renally eliminated, mostly unchanged, and monitoring of renal function is important (**4).**

Pharmacokinetics:

Bioavailability: 50 to 60% for metformin hydrochloride 500 mg tablet based on fasted conditions

- Food effect: Decrease extent of absorption and delays absorption (Cmax 40% lower, AUC 25% lower, Tmax extend by 35 minutes for fed vs. fasted)
- The volume of distribution: 654 ± 358 L for 850 mg strength
- Plasma protein binding: Negligible
- Steady-state plasma concentration: within 24 to 48 hours
- Elimination: Excreted unchanged in the urine (no hepatic metabolism or biliary excretion)
- Elimination half-life: approximately 6.2 hours

Typically at diagnosis of type 2 diabetes, lifestyle management such as diet and exercise are recommended. Metformin is often used as monotherapy or in combination when diet and exercise are not effective at lowering hyperglycemia. According to the American Diabetes Association (ADA), metformin is the preferred first-line agent in patients with type-2 diabetes mellitus in adults and children ten years and older. Per Standards of Medical Care in Diabetes 2018, if a patient's A1c is less than 9% at diagnosis, then metformin monotherapy is recommended. If the A1c is greater than 9%, then metformin is recommended in combination therapy. Metformin is not indicated in type 1 diabetes mellitus(**4).**

In insulin resistance when insulin fails in this effort, glucose levels rise and diabetes ensues. Raised insulin concentrations have a side effect in the body of stimulating the ovary to produce more testosterone. Reducing insulin by diet, weight loss or drugs results in a lowering of testosterone and improvement of symptoms of PCOS. All women with PCOS who are overweight would benefit from a regime of diet reform and exercise. In PCOS, use of metformin is associated with a 10 folds reduction in gestational diabetes (31% to 3). It also reduces insulin resistance and insulin secretion, thus decreasing the secretory demands imposed on pancreatic beta-cells by insulin resistance and pregnancy. Metformin, is a biguanideantihyperglycemic drug, it has been shown to improve hyperandrogenism, hyperinsulinemia, and menstrual cyclicity, most likely through its positive effects on insulin clearance and abdominal adiposity, in both obese and non-obese PCOS patients **(1).**

Recent evidence also suggests that one of the methods of action of metformin may be through phosphorylation of insulin receptor and insulin receptor substrates. In addition, metformin appears to induce cardio-protective effects on serum lipids as well as plasminogen activator inhibitor (PAI)-1 and may decrease the risk of development of type 2 diabetes. Collectively, in PCOS patients, Metformin improves metabolic disorders as a consequence of insulin resistance and subsequent chronic sequalae, hypertension and cardiovascular disease **(2).**

Effect of metformin on reduction of androgens

The primary goal of the treatment of hyperandrogenism is central or peripheral androgen suppression using three groups of drugs:

- Inhibitors of androgen production (oral contraceptives).
- Peripheral androgen blockers (cyproterone acetate, flutamide finasteride, spironolactone).
- Insulin-sensitizing agents (metformin).

In both obese and non-obese PCOS patients, hyperandrogenism can be effectively treated by reducing hyperinsulinemia using metformin. In ovarian theca cells, metformin inhibits androstenedione production with no effect on progesterone. Clinically, metformin therapy results in a significant decrease in the total serum testosterone. Moreover metformin corrects not only ovarian hyperandrogenism but also functional adrenal hyperandrogenism in adolescents with PCOS . Antiandrogens as sole

treatment or combined with metformin has been proven as effective treatments for the manifestations of hyperandrogenemia. Specifically, clinical improvement of hyperandrogenemia was observed more using combined therapy than using a single agent **(4).**

Effect of metformin on ovulation, menstrual cycles and conception

In women with PCOS, elevation of circulating insulin and insulin-like growth factor-1 (IGF-1) levels result in overproduction of androgens in ovarian theca cells. Metformin inhibits production of androgens in theca cells, in part through reducing pituitary secretion of LH leading to ovulation and regular menstrual cycles. Clinically metformin is effective for ovulation induction, menstrual cycle regulation and pregnancy in both obese and non-obese patients with PCOS. Although metformin has been shown to be effective in the treatment of anovulation in women with PCOS, clomiphen citrate (CC) is still considered to be the drug of choice to induce ovulation in these patients. In addition, metformin plus CC appears to be very effective for the achievement of pregnancy compared with CC alone. Metformin also has several non-FDA-approved indications, including gestational diabetes, management of antipsychotic-induced weight gain, type 2 diabetes prevention, and the treatment and prevention of polycystic ovary syndrome (PCOS). Currently, metformin is the only ADA-recommended antidiabetic for pre-diabetes. As for potential indications, researchers are studying metformin for its possible antiaging, anticancer, and neuroprotective effects (**3).**

Administration

Metformin is an oral medication typically dosed from 500 to 2550 mg per day and administered with a meal to decrease GI upset. The daily dose is often titrated weekly in increments of 500 mg or 850 mg to reduce this risk. The recommendations are to take metformin at the same time every day. Extended-release tablets are typically taken once daily with an evening meal and should be swallowed with a full glass of water (**1).**

Recommended Adult Dosing

Treatment of Diabetes Mellitus type 2

The initial dose of 500 mg once or twice a day or 850 mg once a day is recommended for immediate release oral formulation. The daily dose is often titrated weekly in increments of 500 mg or 850 mg to reduce GI adverse effects. The typical maintenance dose is 850mg or 1000 mg twice a day. On the other hand, the initial dose of 500 mg once or 1000 mg once a day is recommended for extended-release oral formulation. This daily dose can be titrated weekly in increments of 500 mg for up to 6 weeks. After that, a maximum dose of 2000 mg once or twice a day is recommended for extended-release formulation (**3).**

Off-labeled Uses

Prevention of Diabetes Mellitus Type 2

The initial dose of 850 mg once a day for a month is recommended for immediate release oral formulation. To achieve the desired outcome, this dose may increase up to 850 mg twice a day (**4).**

Treatment of Antipsychotic-induced Weight Gain

The initial dose of 750 mg up to 2000 mg is recommended in two to three divided doses for immediate release oral formulation. A maximum dose of 2550 mg daily is also used in some studies. For extended-release formulation, the initial dose of 500 mg once is recommended and may be increased by 500 mg every two to six weeks based on the dose tolerability of patients. A maximum dose of 1000 mg to 2000 mg daily is recommended for extended-release formulation (**1).**

Treatment of Gestational Diabetes Mellitus

The initial dose of 500 mg once or twice a day is recommended for immediate release oral formulation. Then, it may increase up to 2000 mg - 2500 mg in two to three divided doses to achieve the glycemic targets. To achieve glycemic targets, the insulin may be coadministered with metformin therapy (**1).**

Effectiveness of metformin for women with PCOS and repeat pregnancy loss remains speculative

Evidence is emerging that abruptly stopping metformin once pregnancy is diagnosed might predispose to pregnancy loss. It has long been debated whether PCOS is an independent risk factor in its own right that contributes to risk of recurrent pregnancy loss, or whether it is purely the association of PCOS with obesity that sees recurrent miscarriage over-represented in women with PCOS, with most authorities now favouring the latter theory of obesity as the cause for this association. Nonetheless early observational data were cited as 'evidence' that metformin may improve the chance of successful pregnancy amongst women with PCOS and recurrent miscarriage, although this remains unproven by RCTs. Metformin resulted in a higher incidence of gastrointestinal (Peto OR 7.75, 95% CI, 1.32 to 45.71), and a lower incidence of non-gastrointestinal (Peto OR 0.11, 95% CI, 0.03 to 0.39), severe adverse effects requiring stopping of medication (**3).**

Side effects:

Metformin has not significant adverse effects; however, it may cause a serious condition called lactic acidosis with the following symptoms: Dizziness, severe drowsiness, muscle pain, tiredness, chills, blue/cold skin, fast/difficult breathing, slow/irregular heartbeat, stomach pain with diarrhea, nausea or vomiting. Lactic acidosis usually occurs due to drug overdose or in some contraindicated conditions. It is more likely to occur in patients with certain medical conditions, including a serious infection, liver or kidney disease, recent surgery, any conditions that cause a low level of oxygen in the blood or poor circulation (such as recent stroke, congestive heart failure, recent heart attack), heavy alcohol use, dehydration, X-ray or scanning procedures that require an injectable iodinated contrast drug and those older than 80 years. Nausea, vomiting, stomach upset, diarrhea, weakness, or a metallic taste in the mouth may occur (**1).**

Metformin usually does not cause hypoglycemia; however, low blood sugar may occur if this drug is used with other anti-diabetic drugs. Hypoglycemia is more likely to occur with heavy exercise, drinking large amounts of alcohol, or not consuming enough calories from food. Serious allergic reaction to this drug is rare; however, this product may contain inactive ingredients, which can cause allergic reactions or other problems. High fever, diarrhea, vomiting, diuretics or excess sweating may cause dehydration and increase the risk of lactic acidosis. Older adults may be at greater risk for side effects such as low blood sugar or lactic acidosis. Gastrointestinal intolerance is one of the most frequently occurred and lactic acidosis is a rare, but causes serious adverse effects. Incidence of myocardial infarction (MI) is also an important event but seen less in metformin compared with sulfonylurea agents (**4).**

A population-based study demonstrated that about one-fourth of patients prescribed metformin had contraindications to its use. However, contraindications rarely resulted in discontinuation of metformin usage. These data have been confirmed by several other studies in different countries. Furthermore, in a review article, based on 347 observational cohort studies and prospective comparative trials, no evidence indicating metformin to be associated with increased levels of lactate or increased risk of lactic acidosis in comparison to other antihyperglycaemic drugs has been reported. In a study sample of 19,691 type 2 diabetes mellitus (DM), patients with established atherothrombosis participating in study, the two-year mortality rate was significantly less in patients treated with metformin compared with the patients not treated with metformin. Therefore, it might be necessary to reconsider the list of contraindications in the use of metformin (**3).**

Orlistat

Orlistat (tetrahydrolipstatin) is a United States Food and Drug Administration (FDA) approved anti-obesity medication. It is a

saturated derivative of endogenous lipstatin isolated from *Streptomyces toxytricini*. The FDA-approved indications of orlistat include (**5)**:

- Patients with obesity with a body mass index (BMI) of over 30 kg/m
- Patients with a BMI greater than 27 kg/m and the presence of risk factors including hypertension, diabetes, and dyslipidemias .
- Reduction of the risk for weight regains after prior weight loss**.**

Orlistat is the saturated derivative of lipstatin, a potent natural inhibitor of pancreatic lipases isolated from the bacterium Streptomyces toxytricini. However, due to its relative simplicity and stability, orlistat was chosen over lipstatin for development as an anti-obesity drug.

The maximum benefit of orlistat occurs when used in conjunction with diet and exercise. The weight starts to decrease within two weeks of initiation of orlistat. Statistically, significant weight loss occurs when orlistat use is for greater than two months. After six months of orlistat use, the mean weight loss is around 5.6 kg compared to 2.4 kg in the placebo group. Orlistat also causes a significant reduction in BMI, waist circumference, total cholesterol, and LDL levels (**6).**

In the XENDOS trial, orlistat has been found to have a statistically significant impact in reducing the incidence of diabetes in patients with impaired glucose tolerance. According to a scientific statement from the American Heart Association in 2021, orlistat is safe and effective for treating obesity with heart failure. A study reported that orlistat is safe and effective in lowering serum triglycerides in children with type 1 hyperlipoproteinemia (**7).**

Mechanism of Action

Orlistat acts by reversibly inhibiting gastric and pancreatic lipases. These lipases have an important role in the digestion of dietary fat. They work by breaking down the triglycerides into absorbable free fatty acids and monoglycerides. Orlistat covalently binds to the serine residues of active sites of lipases and inactivates them. The inactivation of lipases prevents the hydrolysis of triglycerides, and thus free fatty acids are not absorbed (**8).**

The primary action of orlistat is local lipase inhibition within the gut. Systemic absorption is not necessary for the activity of orlistat. At the recommended dosage, orlistat inhibits dietary fat absorption (approximately 30%). According to AHA, the percentage change in weight is also associated with a small reduction in blood pressure (**9).**

Research also suggested that orlistat has a beneficial consequence on carbohydrate metabolism. In addition, obesity increases the risk of hyperuricemia and cardiovascular disease. Meta-analysis results indicated that orlistat significantly reduced serum uric acid levels in adult patients (**10).**

Pharmacokinetics (**9):**

- Absorption: Orlistat acts mainly via its local effect in the gut, and systemic exposure to the medication is minimal.
- Distribution: Most (more than 99%) of the drug is bound to the plasma proteins (lipoproteins and albumin are the major binding proteins).
- Metabolism: Orlistat metabolism is primarily within the intestinal wall.
- Elimination: 95 to 97% of the medication is unabsorbed and excreted in feces.

Administration

Orlistat is available in oral tablets 60 mg (over the counter) and 120 mg (prescription product). The recommended orlistat prescription dose is 120 mg capsule orally thrice daily. The administration should be during or within 1 hour after the fat-containing meal. Doses of more than 120 mg have not shown any additional benefit. The recommendation is that the patient adheres to a nutritionally balanced, low-calorie diet with less than 30% of calories from fat. If the patient misses the meal, they can omit the orlistat dose (**8).**

If the patient misses the dose of orlistat and it has been more than 2 hours past the fat-

containing meal, then the patient can skip that dose since, by that time, most of the fat absorption has already occurred, and the medication would not work effectively. Since orlistat reduces the absorption of fat-soluble vitamins, patients should take multivitamin supplements(containing fat-soluble vitamins) daily. Administration of multivitamin supplements should be at a gap of more than 2 hours after the orlistat administration. Healthcare professionals must rule out organic causes of obesity like hypothyroidism or Cushing syndrome before initiating orlistat therapy (**8).**

Use in Specific Patient Population

- **Renal Impairment:** Orlistat is safe in patients with renal impairment.
- **Hepatobiliary Disease:** Orlistat use requires caution in patients with obstructed bile ducts and deranged liver function tests.
- **Pregnancy Considerations:** Orlistat is contraindicated in pregnancy. It is a former FDA pregnancy category X drug. Patients on orlistat therapy should be counseled regarding the necessity for contraception. According to USPTSF(The United States Preventive Services Task Force), limiting the gestational weight gain(GWG) in pregnancy is associated with a reduced risk of emergency cesarean delivery, gestational diabetes mellitus, and macrosomia. For limiting GWG, behavioral interventions are advised rather than pharmacotherapy (**9).**
- **Breastfeeding Considerations:** Orlistat is minimally absorbed, and a small amount has been detected in the milk. Orlistat inhibits the absorption of fat-soluble vitamins; breastfeeding mothers should take a multivitamin supplement (containing fat-soluble vitamins). It is doubtful that the infants absorb orlistat in an amount that adversely impacts the breastfed infant. Manufacturer labeling advises caution when orlistat is administered during lactation, and clinical practice guidelines don't recommend weight-management medications during breastfeeding (**8).**

Adverse Effects

The side effects of orlistat include the following:

- **Gastrointestinal:**
  The most common side effect of orlistat use is steatorrhea, which occurs because of the impaired absorption of dietary fat. Other side effects include fecal spotting, diarrhea, abdominal pain, and anal fissures. The gastrointestinal adverse effects decrease with ongoing orlistat therapy. These adverse effects can be minimized by following a hypocaloric and low-fat diet with less than 30% of the calories from fats. Rarely, orlistat correlates with cholelithiasis, pancreatitis, and acute cholestatic hepatitis. However, orlistat has been shown to reverse steatosis in patients with non-alcoholic fatty liver disease (NAFLD). Orlistat inhibits the absorption of fat-soluble vitamins and other fat-soluble nutrients. Patients should use a multivitamin tablet containing vitamins A, D, E, K, and beta-carotene once daily (**10).**
- **Hepatotoxicity:**
  Cases of hepatotoxicity range from serum enzyme elevations to a few cases of fatal hepatic failure & the requirement for emergency liver transplantation. The proposed mechanism for hepatotoxicity is hypersensitivity, as only a small amount of orlistat is absorbed. However, clinical features of hypersensitivity are absent in orlistat-induced hepatotoxicity (**8).**
- **Renal:**
  Orlistat can increase the risk of acute kidney injury; this occurs because the unabsorbed fat binds with calcium in the intestinal lumen resulting in excessive oxalate, which is absorbed and deposited in the kidney leading to oxalate

nephropathy and increased risk of renal stones (**9).**

- **Musculoskeletal:**
  Theoretically, orlistat can increase the risk of osteoporosis because of impaired absorption of calcium and vitamin D.
- **Oncology:**
  Animal studies have shown an increased risk of colorectal cancer with orlistat. However, in humans, no such association has been elucidated. Orlistat is known to inhibit the synthesis of fatty acid synthase (Fas) enzyme, which increases tumor growth. In addition, orlistat has been shown to have anti-neoplastic activity in ovarian cancer cells, breast cancer cells, and prostate cancer cells in various animal studies. Few case reports have illustrated the association of orlistat use with hypertension, diabetic ketoacidosis, depression, cutaneous vasculitis, lichenoid eruptions, and vaginitis. However, a causal relationship between orlistat and these adverse effects remains unproven (**6).**

Drug Interactions

Antiepileptics: Orlistat can reduce the absorption of lipophilic antiepileptics like lamotrigine, valproate, vigabatrin, and gabapentin, resulting in a decrease in plasma concentration. In such cases, it is recommended to monitor antiepileptic medication levels (**7).**

- Amiodarone: Orlistat can reduce the absorption of amiodarone
- Cyclosporine: Orlistat can also reduce the absorption of cyclosporine (immunosuppressant). Therefore, the recommendation is that the administration of these two medications should be at a gap of at least 2 hours. Also, the cyclosporine levels require monitoring in patients taking the medication along with orlistat (**8).**
- Levothyroxine: Orlistat can bind with levothyroxine in the gut and reduce its absorption, leading to decreased plasma concentration of levothyroxine and subsequent hypothyroidism. Thus, clinicians should advise patients to take levothyroxine and orlistat at least 4 hours apart (**7).**
- Warfarin: Using orlistat along with warfarin can result in prolonged prothrombin time and INR because orlistat reduces the absorption of vitamin K. Therefore, coagulation parameters require monitoring in patients taking these two medications together (**9).**
- Antiretroviral medications: Orlistat also reduces the absorption of antiretroviral drugs; monitoring of HIV viral load is necessary. If the HIV viral load increases, orlistat should be discontinued (**8).**

Contraindications

Contraindications to orlistat include the following conditions (**10)**:

- Hypersensitivity to orlistat or its constituents
- Chronic malabsorption
- Cholestasis
- Anorexia and bulimia
- Pregnancy
- Severe renal impairment
- Use with caution in patients with anorexia or bulimia nervosa

Monitoring

- It is necessary to monitor the body weight, body mass index (BMI), waist circumference, and lipid profile in patients taking orlistat.
- The levels of cyclosporine, antiepileptic, and HIV viral load require monitoring when using orlistat in conjunction with these medications (**6).**
- Patients with diabetes might need to adjust the dose of diabetes medicine, as weight loss can affect glycemic control.
- Monitor the impact of Weight loss on Quality of Life-Lite (IWQOL-Lite), a widely used tool in assessing weight-loss interventions in clinical trials (**8).**

- According to the (AACE/ACE) American Association of Clinical Endocrinologists, Medical Guidelines & American College of Endocrinology guidelines, patients receiving orlistat should be monitored for cholelithiasis in patients with mild hepatic impairment. In patients receiving orlistat, there is a risk of nephrolithiasis; monitor for flank pain and hematuria (**9).**

Toxicity

There is no specific antidote for orlistat overdose. However, if a significant overdose of orlistat occurs, the patient should immediately come to the emergency department and be observed for 24 hours to provide supportive care. There is a report of overdose with 5160 mg orlistat in a 28-month-old baby. The patient did not experience any adverse events and was discharged from the emergency room without any concerns (**10).**

In a study involving 105 pediatric patients. Orlistat exposures among young children were managed by decontamination and had optimistic outcomes with few gastrointestinal adverse clinical effects (**6).**

Orlistat in polycystic ovarian syndrome

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy of women with a prevalence of 6-10% based on the National Institute of Health criteria and as high as 15% when the broader Rotterdam criteria are applied (**8).**

Obesity has reached it epidemic proportion. Its is present in 40-60% of women with PCOS mostly of central type. Weight loss is the first-line treatment evidence-based approach in overweight PCOS women (**7).**

Pharmacotherapy aiming to achieve weight loss for the group of obese PCOS patients comprises use of insulin-sensitizing drugs such as metformin and use of antiobesity drugs like orlistat (**6).**

There have been few randomized studies, which have compared the effects of orlistat and metformin in obese PCOS patients and have generally reported favorable results with equal efficacy of both drugs on weight reduction (**7).**

Orlistat being long acting and gastric lipase inhibitor which prevent the hydrolysis of dietary fat into absorbable free fatty acids and monoglyceride with increase of fecal fat excretion. Metformin insulin sensitizers various other mechanisms have been proposed (**8).**

In a previous study, statistically significant weight loss in terms of weight, BMI, waist circumference and waist-hip ratio was achieved with the degree of decline being same in both metformin and orlistat arms (*P* - 0.418) compared to the control arm. It is similar to results in previous studies by Metwally *et al*. and Ghandi *et al* (**9).**

The pilot study in 2005 by Jayagopal *et al*. demonstrated that those on orlistat showed more significant reduction in weight compared to metformin with *P* - 0.002 for orlistat versus 0.006 for metformin (**10).**

The result of a previous suggests that both orlistat and metformin can induce ovulation in overweight and obese PCOS women at similar rates (33.3% vs. 23.3%, *P* - 0.418). These results are consistent with previous studies by Metwally *et al*. and Ghandi *et al* (**6).**

The best predictor of ovulation according to the present and the previous study is percentage weight loss and a low concentration of baseline LH (**5).**

A previous study demonstrated a statistically significant fall in total serum testosterone levels and improvements in the FAI in both drug arms (**6).**

Similar to the results of a previous study Metwally *et al*. and Jayagopal *et al*. found a significant decrease in the values of total testosterone and FAI in both the orlistat and metformin group (**7).**

In a previous study treatment with orlistat produced significant change in the lipid parameters including significant fall in total

cholesterol, LDL cholesterol and triglycerides ($P < 0.05$), whereas subjects in metformin and control arm showed no change in lipid profile (**6).**

In a previous study, none of the groups showed improvement in any of the biochemical parameters for assessing insulin resistance. Nevertheless, there was fall in levels of fasting blood sugar, fasting insulin and HOMA-IR in the metformin group but it did not reach the level of significance (**7).**

When plasminogen activator-1 (PAI-1) levels were analyzed in a study, orlistat did not show any reduction in PAI-1, compared with metformin. The reduction in circulating androgens during Metformin treatment might be implicated in this decline (**8).**

A study on 101 PCOS woman showed orlistat combined with lifestyle changes induces substantial weight loss in PCOS. However, emphasis on lifestyle changes when combined with anti-obesity agents, exert beneficial effects on the endocrine abnormalities of obese patients with PCOS and improve metabolic parameters(**9).**

A study with, 24 weeks of orlistat with diet and physical exercise resulted in significant weight loss, improvement of hyperandrogenism and insulin sensitivity and increased anti-Müllerian hormone levels. The importance of lifestyle modification should be stressed before initiation of pharmacological intervention (**10).**

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