

## Review Article

# Pharmacological Treatment of Obesity in Patients with Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) is a common disorder affecting women of reproductive age and it is associated with increased cardiovascular risk. Obesity plays an important role in the pathogenesis of PCOS, and the majority of patients with PCOS are obese. Over the last 20 years, the prevalence of obesity has dramatically increased, with probable associated increase in PCOS. Weight reduction plays an integral part in the management of women with PCOS. In this paper, current available weight reduction therapies in the management of PCOS are discussed.

## 1. Introduction

Polycystic ovary syndrome (PCOS) is a common disorder with a prevalence of 6-7% of women of reproductive age [1-4]. The clinical picture commonly includes obesity, hirsutism, oligomenorrhoea, and subfertility. Around 30-75% of PCOS women are obese [1, 5, 6], and many PCOS women show evidence of insulin resistance and hyperandrogenism. In 2003, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) cosponsored the Rotterdam polycystic ovary syndrome consensus workshop that revised and broadened the National Institute of Health (NIH) 1990 diagnostic criteria [7].

While chronic anovulation with biochemical and/or clinical hyperandrogenism is essential for making the diagnosis under the NIH 1990, classic PCOS, [8] the revised Rotterdam criteria [7] (box 1) included women with hyperandrogenism but regular menses and those with menstrual disturbance without overt androgen excess, nonclassic PCOS. The revised Rotterdam criteria, although commonly, used are still controversial and reflect the heterogeneous presentation of the syndrome and the advances in understanding its uncertain aetiology [9].

## 2. The Role of Obesity in the Development of PCOS

The exact role that obesity plays in the development of PCOS remains to be determined. The theories that have been put forward to explain the metabolic abnormalities associated with obesity may also be applicable to explain the role of obesity in the development of PCOS.

The adipokine theory suggests that the adipose tissue is an endocrine organ that secretes several hormones (adipokines). Insulin resistance and hyperandrogenism are common features of PCOS [7, 10]. Alteration in adipokines levels may lead to the development of PCOS. Adiponectin is exclusively produced by the adipose tissue [11]. Several studies have shown adiponectin to be lower in PCOS women when compared to weight-matched controls [12, 13]. Adiponectin is inversely related to insulin resistance [14]. While some studies suggest a strong correlation between adiponectin and androgen levels in PCOS [13], others did not show similar association [12]. Leptin is not produced exclusively by adipocytes but its circulating levels are strongly correlated to adipose mass and are higher in obese people [15]. In most studies, leptin levels in PCOS were similar to those of controls of similar body weight [16]. Whether leptin

Two of the following three criteria must be fulfilled:  
 (i) A clinical diagnosis of oligomenorrhoea or amenorrhoea  
 (ii) Clinical or biochemical evidence of hyperandrogenism  
 (iii) Polycystic ovaries on ultrasound examination (either 12 or more follicles measuring 2–9 mm in diameter, or an ovarian volume of >10 cm<sup>3</sup>)

Late onset congenital adrenal hyperplasia, androgen secreting tumours, and Cushing's syndrome must be excluded in women with raised androgens; thyroid disorders and raised prolactin should be excluded in women with menstrual disturbances.

ALGORITHM 1: Revised 2003 criteria for diagnosing polycystic ovary syndrome (PCOS) [7].

levels in PCOS are associated with androgen levels remains controversial [17, 18]. Hyperleptinaemia has been associated with insulin resistance [17] and is inversely related to fertility in PCOS women [19]. Resistin is another adipokine and its relationship to PCOS remains debatable. Increased levels of resistin have been linked to the development of insulin resistance [20] and may play a role in the development of cardiovascular disease [21]. However, while some studies suggest increased levels in PCOS [16], others showed PCOS women to have similar levels when compared to weight-matched controls [13].

On the other hand, the adipose tissue expandability theory [22] proposes that at a set point of positive energy imbalance, which is determined on an individual basis by genetics and environmental factors, the subcutaneous adipose tissue fails to expand to store more fat subcutaneously. This results in a state of lipotoxicity and fat starts to deposit in other tissues like the liver, muscles, and pancreas. Lipotoxicity drives insulin resistance and subsequently hyperandrogenism commonly seen in PCOS women [23].

One of the difficulties that face any theory trying to explain the origin of PCOS is that it is not one entity. Women with PCOS are not all obese or insulin resistant [24], and the presence of hyperandrogenism and oligo/amenorrhoea is not necessary for making the diagnosis.

### 3. Obesity and Cardiovascular Disease in PCOS

Many cardiovascular (CV) risk factors are increased in PCOS even after adjusting for weight. For example, women with PCOS have impaired glucose tolerance [25], dyslipidaemia [26], endothelial [27] and platelets dysfunction [28], lower adiponectin [12], and higher homocysteine levels [18]. Despite the lack of long-term CV outcome data, it has been suggested that PCOS women have a sevenfold increase in relative risk for myocardial infarction [29], higher prevalence of cerebrovascular disease [30], and worsening CV event-free survival [31].

Obesity contributes to the 43% prevalence of the metabolic syndrome in PCOS patients [32]. Central obesity is often associated with PCOS [33] and carries increased risk for developing cardiovascular disease and type 2 diabetes [34].

Over the past 2 decades, the rate of obesity has raised threefold [25]. Whether there is an increase in the prevalence

of PCOS to parallel the increase in obesity is still controversial [35, 36].

### 4. Treatment of Obesity in the Setting of PCOS

Even modest weight loss of less than 10% of initial body weight has been shown to increase the frequency of ovulation, improve conception, and reduce testosterone, free androgen index, hyperlipidaemia, hyperglycaemia, and insulin resistance in women with PCOS [37, 38].

*4.1. Life Style Changes.* Lifestyle modification is regarded as the first line treatment for women with PCOS. Exercise and weight loss improve insulin sensitivity. 44–57% of PCOS women had improvement in either menstrual cycle or ovulation after lifestyle changes and subsequent weight loss [37, 39, 40]. One of the main challenges of lifestyle changes is the low participants' compliance rate over time [39]. Therefore, pharmaceutical intervention is an additional essential therapeutic tool to lifestyle changes in many patients.

*4.2. Medical Therapy.* Few safe and effective drugs are currently available for the treatment of obesity. Although Sibutramine [41] and rimonabant [42] have been shown to be effective in inducing weight loss in PCOS women, they have both been withdrawn from the UK. Rimonabant increased the risk of psychiatric disorders and sibutramine has been associated with hypertension and cardiovascular disease.

*4.2.1. Orlistat.* Orlistat is a lipase inhibitor that reduces fat absorption in the gut by approximately 30% [43]. In a meta-analysis, it is estimated that orlistat treatment led to an average placebo-subtracted weight loss of 2.7 kg at 1 year [44]. In a 4-year randomised controlled trial of 3305 obese, nondiabetic patients, orlistat treatment was associated with a 3.6-kg weight loss compared with 1.4 kg for placebo at 4 years [45].

In women with PCOS, a 4.69% weight reduction was reported with orlistat therapy with an associated improvement in total testosterone levels [46]. In a 12-week randomised open labelled study [47], orlistat reduced insulin resistance by around 20% and variability of insulin resistance by 40% in obese PCOS women. In a 6-month clinical trial, therapeutic intervention with orlistat and a low-calorie diet

resulted in a beneficial effect in PCOS in reducing advanced glycation end-products (AGE) levels and testosterone concentrations independently of BMI changes [48].

The use of orlistat is limited by its gastrointestinal side effects. Approximately, 15–30% of those taking orlistat experience oily stool, faecal urgency, or oily spotting, and 7% report faecal incontinence, particularly at the initiation of treatment [44]. Despite its relatively high rate of side effects, orlistat is a useful treatment tool in the management of obese PCOS women.

**4.2.2. Metformin.** Metformin is a biguanide commonly used for the treatment of type 2 diabetes. Metformin's primary action is on the liver, where it reduces gluconeogenesis. Extrahepatic sites of action include the skeletal muscles, adipose tissue, endothelium, and the ovary [49, 50]. Metformin is commonly used in women with PCOS and is reported to improve insulin resistance, sex hormone binding globulin (SHBG), hyperandrogenaemia, and ovulation [51, 52]. Metformin's effect on weight management remains controversial. In a small ( $n = 56$ ) randomized, double-blinded, placebo controlled cross-over study, 6-month treatment with Metformin resulted in mean weight reduction of 2.3 kg ( $P < .009$ ) [53]. However, in a systematic review and meta-analysis [54], metformin was found to have no effect on body weight and body mass index (BMI) in women with PCOS. Metformin may be more effective in subgroups of PCOS women and at higher doses. Nonobese women with PCOS responded better to metformin than obese women with regards to insulin sensitivity, free testosterone, and androstendione concentrations [55]. Metformin was also found to cause a dose-related weight loss in obese women with PCOS [56], (1.5 and 3.6 kg weight loss in 1500- and 2550-mg/day metformin treated groups, resp.). Metformin when given to obese PCOS women after rimonabant, an endocannabinoid blocker, maintained the weight reduction and decrease in waist circumference achieved by rimonabant and augmented the initial improvements in testosterone levels and insulin resistance [57]. It is possible that the insulin sensitisation action of metformin was complementary to the weight loss caused by rimonabant.

Most frequent side effects of metformin are gastrointestinal symptoms including nausea, anorexia, vomiting, abdominal discomfort, and diarrhoea and occur in up to 20% of patients. In 3–5% patients, therapy may have to be discontinued because of these adverse effects [50, 58]. Slow release forms of metformin are available and are believed to be better tolerated.

Despite the lack of strong evidence, the use of metformin in obese PCOS women is likely to be beneficial especially when taken at higher doses.

**4.2.3. Incretin Mimetics Therapy.** The gastrointestinal tract produces several peptide hormones that participate in regulation of food intake. Ingested nutrients, especially fats and carbohydrates, stimulate Glucagon-like peptide-1 (GLP-1) secretion from L cells in the distal small intestine [59]. GLP-1 accentuates glucose-dependent insulin release,

inhibits glucagon secretion, increases pancreatic  $\beta$  cell growth, suppresses appetite and energy intake, and delays gastric emptying [60–63]. Glucagon-like peptide-1 receptor (GLP-1R) is expressed by the gut, pancreas, brainstem, hypothalamus, and vagal-afferent nerves [60]. Activation of the hypothalamic GLP-1R decreases food intake [64].

In a 24-week randomised controlled trial in women with PCOS [65], a combination treatment with exenatide (GLP1 mimetic) and metformin was found to be superior to exenatide or metformin monotherapy in reducing weight (mean weight loss of  $6 \pm 0.5$  kg) and improving menstrual cycles, ovulation rate, free androgen index, and insulin sensitivity.

In another 20-week randomised open labelled study involving obese people without PCOS [66], comparing liraglutide (GLP1 analogue) to orlistat, it was shown that liraglutide treatment is well tolerated and induced significant dose-related weight loss (mean weight loss 4.8–7.2 kg) compared to placebo or orlistat. All the patients were obese and had a 500 kcal per day energy deficit diet and increased their physical activity throughout the study.

In a head-to-head comparison study in people with type 2 diabetes, 1.8 mg liraglutide daily and 10  $\mu$ g exenatide twice daily produced similar weight loss (3.2 kg with liraglutide versus 2.9 kg with exenatide) [67]. However, liraglutide achieved better glycaemic control and was better tolerated than exenatide [67].

Most commonly reported side effects are nausea and vomiting, but the main safety concern remains a possible increased risk of pancreatitis attributable to drugs that act through the GLP-1 pathway [68]. One of the disadvantages of using GLP-1R agonists is that they require injection. Although, not yet licensed for obesity management, GLP-1R agonists offer a potential obesity treatment for women with PCOS.

**4.2.4. Bariatric Surgery.** In subjects with morbid obesity, bariatric surgery may be considered as an effective therapy. Few studies have shown bariatric surgery to be associated with significant improvement in weight, hirsutism, insulin resistance, and fertility in women with PCOS [69, 70].

## 5. Conclusions

PCOS is a common disorder of uncertain aetiology. It is associated with increased cardiovascular morbidity. Obesity plays an important part in the pathogenesis of PCOS. Many PCOS women are obese, and weight reduction is an essential part in their management.

In the management of obese women with PCOS, lifestyle modification is the first step although low long-term compliance rate may reduce benefit. Orlistat, with dietary changes, is beneficial despite its common gastrointestinal side effects. Metformin, at higher doses, may promote weight loss. Although not currently licensed, newer pharmacotherapeutic agents like incretin mimetics hold promise in managing obese women with PCOS.

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