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The Use of GLP-1 Receptor Agonists in the Treatment of Obesity in Women with PCOS

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ABSTRACT

Introduction and aim of study: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting young women. It is diagnosed in individuals who meet 2 of the following 3 criteria: hyperandrogenism, ovarian dysfunction or polycystic ovarian morphology on ultrasound. A common component of this disease is obesity that leads to many serious health complications. This review paper aims to discuss the use of glucagon-like peptide-1 (GLP-1) receptor agonists as a therapeutic option to treat obesity in female patients with PCOS.

Materials and Methods: The authors conducted a comprehensive review of the literature available in databases: PubMed and Medline focusing on the terms “PCOS”, “GLP-1”, “obesity”.

Results: The first-line treatment of metabolic disorders in the course of PCOS is lifestyle modification. In patients who do not achieve sufficient results pharmacotherapy is recommended. Therapy with GLP-1 receptor agonists shows beneficial effects not only on weight loss, but also on metabolic and endocrine disorders. Studies have proven the superiority of these medications over metformin in the treatment of obesity associated with PCOS. However, the simultaneous use of GLP-1 receptor agonists and metformin may be beneficial for the patients.

Conclusions: GLP-1 receptor agonists appear to be a promising therapeutic option in obese women with PCOS according to safety profile and effectiveness proven in studies.

KEY WORDS: Polycystic Ovary Syndrome, Obesity, Glucagon-Like Peptide-1 Receptor Agonists

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in premenopausal women. The prevalence of this syndrome varies depending on the country and the diagnostic criteria used, ranging from 6% to 20%. [1] PCOS is characterized by a constellation of symptoms and clinical features, including hyperandrogenism (clinical or biochemical), ovarian dysfunction (oligo-ovulation or anovulation), and polycystic ovarian morphology on ultrasound. According to the Rotterdam criteria, PCOS can be diagnosed in a woman who meets 2 out of these 3 clinical features. [2] Additionally, diagnosis is possible after excluding other syndromes with similar symptoms, such as hyperprolactinemia, congenital adrenal hyperplasia, or Cushing's syndrome. [3] A familial occurrence of PCOS is also observed. Furthermore, PCOS is considered one of the leading causes of infertility associated with anovulation. [4]

PCOS is closely linked with metabolic disorders such as obesity, insulin resistance with compensatory hyperinsulinemia. [5] Obesity occurs in 40–70% of patients with this endocrinopathy. [6] It is also noteworthy that insulin resistance is present in the majority of lean women with PCOS. [6] The consequences of these metabolic disorders include an increased risk of type 2 diabetes, hypertension, dyslipidemia, and cardiovascular diseases. Increasing emphasis is placed on lifestyle modifications in the management of PCOS. Effective weight control is a key element in the therapy of PCOS patients to improve metabolic parameters and reduce the risk of developing diabetes and cardiovascular diseases. [3] In recent years, glucagon-like peptide-1 (GLP-1) receptor agonists have garnered increasing interest in the context of obesity treatment, including among women with PCOS. These substances, initially used mainly in the treatment of type 2 diabetes, demonstrate several beneficial metabolic effects, including the ability to reduce body weight. [7]

This paper aims to review the literature on the use of GLP-1 receptor agonists in the treatment of obesity in women with PCOS. Two databases, PubMed and Medline, were searched using the terms "obesity," "PCOS," and "GLP-1," yielding 95 results. The publications were analyzed for the relationship between obesity and PCOS, the mechanism of action of GLP-

1 receptor agonists, their effectiveness in treating obesity and other metabolic disorders in women with PCOS, and the potential benefits and risks associated with their use in this specific group of patients.

ETIOLOGY AND PATHOPHYSIOLOGY OF PCOS

PCOS is considered to have a multifactorial etiology, comprising genetic, epigenetic, and environmental factors. [6] Insulin resistance and the associated hyperinsulinemia are deemed key pathological factors in the development of PCOS, with obesity being the most common cause of insulin resistance. [8] Therefore, all environmental factors that can lead to overweight or obesity and alter insulin action, especially those related to lifestyle, inadequate diet, and lack of physical activity, may contribute to this endocrinopathy. Other non-genetic factors include exposure to endocrine-disrupting chemicals and excess androgens. [8] Many studies suggest that genetic factors also play a significant role in the etiology of this syndrome. Recent genome studies conducted in various populations of women with PCOS have identified several loci strongly associated with the development of PCOS. The genes located in these susceptibility sites are linked to the gonadotropin axis, ovarian androgen production, glucose metabolism, vesicular transport, and receptor recycling, as well as cell cycle regulation. [9, 10] Furthermore, epigenetic modifications of specific promoters, including in response to excessive androgen exposure during the perinatal period, alter gene expression patterns and may increase the risk of developing PCOS. [8]

Hyperandrogenemia is considered the main clinical feature of PCOS, characterized by increased synthesis of ovarian (produced by theca cells) and to a lesser extent, adrenal androgens. [11] Hyperandrogenemia can be caused by increased stimulation of production through high luteinizing hormone (LH) levels relative to follicle-stimulating hormone (FSH) levels and hyperinsulinemia. It also results from decreased conversion of androgens to estrogens in granulosa cells due to reduced enzyme activity. [12] It is estimated that over 80% of women with hyperandrogenism symptoms, including hirsutism, seborrheic changes, acne, or alopecia, have PCOS. [13] The most common biochemical disturbance in PCOS patients is elevated circulating testosterone and androstenedione levels. [14] Hyperandrogenism is associated with impaired reproductive function and metabolic homeostasis. [12] Androgens change the pattern of fat distribution from female to male type, with predominant abdominal obesity, which is consequently associated with hyperinsulinemia and insulin resistance and can result in type 2 diabetes, dyslipidemia, and increased cardiovascular disease risk. [12]

Additionally, in adipose tissue, testosterone is converted to estrogens, and their high levels disrupt the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, leading to increased LH secretion from the pituitary. [12, 15] Elevated androgen levels induce the growth of preantral follicles and increase follicle recruitment, promoting the secretion of anti-Müllerian hormone (AMH) from granulosa cells. Both high AMH and androgen levels inhibit folliculogenesis and increase aromatase activity, resulting in follicle arrest at the antral stage and the development of polycystic ovarian morphology, leading to ovulation disturbances such as oligo-ovulation or anovulation. [16, 17]

Insulin resistance and the associated hyperinsulinemia play a significant role in the pathogenesis of PCOS and are characteristic of both lean and obese women with PCOS. Insulin stimulates pulsatile GnRH and LH secretion and, like androgens, in excess, inhibits follicle growth and maturation, lowering sex hormone-binding globulin (SHBG) levels, leading to increased free testosterone levels. [15] Unlike other organs, the adrenal glands and ovaries maintain their response to insulin in insulin resistance, leading to increased androgen production. [18] Studies have shown that using insulin-sensitizing drugs, such as metformin, reduces circulating insulin and androgen levels, increases SHBG levels, and improves ovarian function in women with PCOS. [19] PCOS patients often exhibit elevated levels of inflammatory markers and oxidative stress. Chronic inflammation may also contribute to insulin resistance and other metabolic abnormalities associated with PCOS. [12] The pathomechanism of PCOS is depicted in Figure 1. [3]

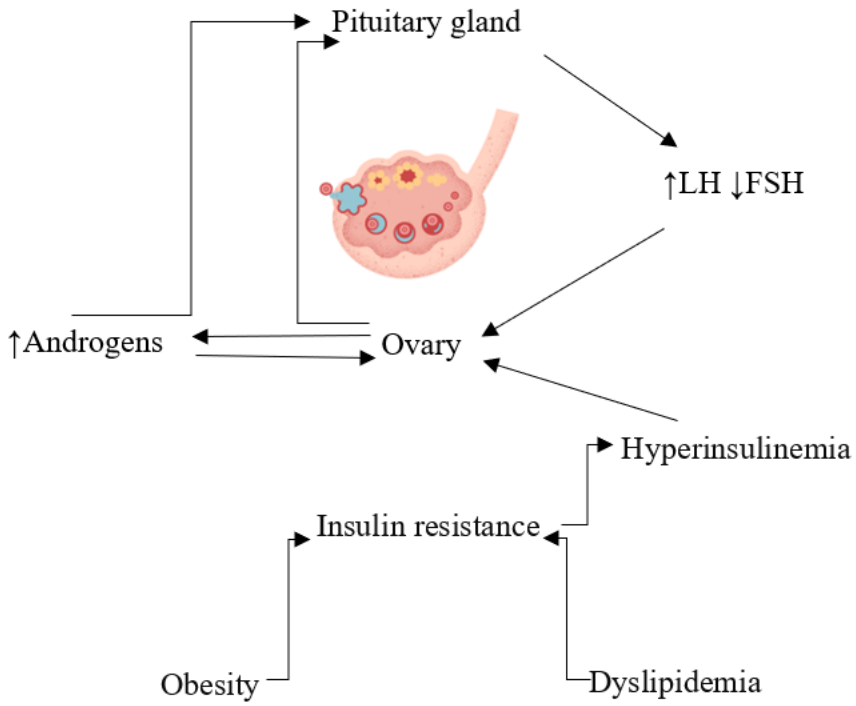

Figure 1. Pathomechanism of PCOS. [3]

OBESITY AND PCOS

Obesity is a common problem among women with PCOS, affecting 50-80% of patients. The interplay between PCOS and obesity is multifaceted, and obesity can be both a cause and a consequence of PCOS. [3, 20, 21] The development of obesity in this endocrinopathy is contributed by concomitant insulin resistance, hyperinsulinemia, hyperandrogenism, dysregulation of the hypothalamic-pituitary-ovarian axis, and environmental factors. Conversely, weight gain and obesity can contribute to the development of PCOS. Obesity causes functional disturbances of the hypothalamic-pituitary-ovarian axis. [12] Excess adipose tissue is responsible for the aromatization of androgens to estrogen, leading to disruptions in hypothalamic GnRH release and consequently increased LH production relative to FSH. These changes account for ovulatory dysfunction and menstrual irregularities. [12, 17] Obesity is also associated with numerous complications and comorbidities, including diabetes, cardiovascular diseases, and obstructive sleep apnea, worsening the prognosis for patients. Therefore, it is crucial for PCOS patients to maintain a healthy body weight and adequate visceral fat levels. [22] Research indicates that weight loss in women with PCOS who are overweight or obese, results in improved insulin sensitivity and reduced serum insulin levels, positively impacting

the metabolic profile. Additionally, improvements in reproductive function (e.g., restoration of ovulation, menstrual cycles, and fertility) and reduction in androgenic symptoms are achieved. [23]

TREATMENT OF OBESITY IN PCOS

The treatment of PCOS focuses on reducing the severity of hyperandrogenism, improving metabolic parameters, decreasing the risk of endometrial hyperplasia and cancer, treating infertility, and inducing ovulation. [3] However, treating obesity in women with PCOS is also a key component, contributing to improved insulin sensitivity, reduced androgen levels, and enhanced fertility. [23] A weight loss of 5–10% improves clinical outcomes (both reproductive and metabolic) in women with PCOS. [24] The first therapeutic option for treating metabolic disorders associated with PCOS is a well-balanced diet and regular physical activity aimed at weight loss and improving metabolic homeostasis. [3] However, most obese patients with PCOS do not achieve significant weight loss through lifestyle changes alone. [25] For these patients, the use of insulin-sensitizing drugs is the preferred therapeutic approach to break the cycle of obesity-insulin resistance-hyperandrogenemia. The main pharmacological treatment includes the use of metformin, which has been shown to improve insulin sensitivity, normalize glucose levels, prevent type 2 diabetes, regulate menstrual cycles, and reduce androgen levels. [26] However, metformin therapy has a moderate effect on weight and obesity, prompting the search for more effective alternatives in treating obesity in PCOS patients. [27] Glucagon-like peptide-1 (GLP-1) analogs are among the new medications used in patients with type 2 diabetes, improving glycemic control and insulin resistance, as well as supporting weight loss. Studies have shown that treatment with GLP-1 receptor agonists not only reduces body weight but also regulates menstrual cycles and improves hyperandrogenemia in obese women with PCOS. [28] Thus, the use of GLP-1 receptor agonists shows promising effects in therapy, not only in terms of weight reduction but also in improving the metabolic profile and hormone levels of patients. Additionally, there are studies on the beneficial effects of weight reduction in patients using sodium-glucose cotransporter-2 (SGLT-2) inhibitors or orlistat, although their use in treating obesity in PCOS is limited. [29] There are also surgical methods for treating obesity, which are among the most effective but also the most burdensome methods for patients. When treating obesity in PCOS, it is essential to remember that a holistic approach, including psychological support, is required.

MECHANISM OF ACTION OF GLP-1 RECEPTOR AGONISTS

Glucagon-like peptide-1 (GLP-1) is one of the main human incretins. Incretin hormones are produced in specialized enteroendocrine cells and enhance meal-stimulated insulin release after food intake. [30] GLP-1 is present in the intestines, brainstem, and, to a lesser extent, in the hormone-secreting pancreas, exerting its effects, including energy balance control, via a single, well-characterized GLP-1 receptor (GLP1R). [31] GLP-1 receptors are expressed throughout the central nervous system, from the olfactory bulb to the spinal cord, in pancreatic islets, the heart, blood vessels, and kidneys. [32] It has been observed that GLP-1 analogs significantly reduce body weight, which is also associated with improved insulin sensitivity. It is suggested that GLP-1 receptor agonists may modulate molecular pathways, including those related to inflammation, oxidative stress, lipid metabolism, and insulin activity. [28] They have multifaceted effects leading to weight reduction, such as decreasing glucagon secretion in pancreatic alpha cells, shortening gastric emptying time, and reducing appetite, resulting in weight loss. [33] The primary indication for GLP-1 analogs was initially type 2 diabetes, but currently, for selected GLP-1 analogs, the registered indication includes obesity treatment. The mechanism of action of GLP-1 receptor agonists is illustrated in Figure 2. [34]

	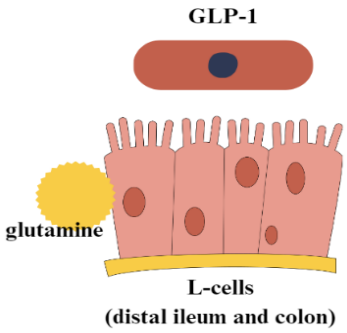
Brain 	↓ Appetite ↓ Food intake ↑ Nausea
Pancreas 	↑ Insulin secretion ↓ Glucagon
Stomach 	↓ Gastric emptying
Adipose tissue 	↑ Lipolysis
Heart 	↑ Cardioprotection
Kidney 	↑ Natriuresis ↑ Diuresis

Figure 2. Mechanism of action of GLP-1 receptor agonists. [34]

EFFICACY OF GLP-1 RECEPTOR AGONISTS IN TREATING OBESITY IN WOMEN WITH PCOS

Obesity is present in most patients with PCOS, and studies show that a weight loss of 5-10% can bring many benefits in terms of metabolic profile and fertility. [35] The role of GLP-1 agonists has been evaluated in studies, both as monotherapy and in combination with

metformin. Significant weight loss was observed in women with PCOS after treatment with liraglutide. The average weight loss, with a mean treatment duration of 27.8 weeks, was 9.0 kg. Similarly, a significant average reduction in BMI of 3.2 kg/m² was noted. A total of 81.7% of patients lost more than 5%, and 32.9% lost more than 10% of their initial weight. [36]

Metformin is the first choice in treating insulin resistance and type 2 diabetes. [37] Both GLP-1 receptor agonists and metformin have beneficial anti-obesity effects in patients with concomitant PCOS. However, meta-analyses suggest that liraglutide had an advantage over metformin in improving insulin sensitivity, reducing BMI, and decreasing waist circumference. A significantly higher percentage of patients achieved 5% and 10% weight loss with GLP-1 treatment (84.2% and 57.8%, $p = 0.01$ and $p = 0.02$) compared to metformin. However, GLP-1 analogs had the same therapeutic effect as metformin in lowering testosterone levels or the free androgen index. No clear differences were found between the groups when the following parameters were compared: improvement in menstrual frequency, SHBG concentration, androstenedione, LH, lipid profile, fasting glucose, fasting insulin, blood pressure. Studies also suggest the beneficial effects of simultaneous use of GLP-1 agonists and metformin. [38, 39, 40]

The psychological aspect plays an important role in treating PCOS. During liraglutide treatment, in addition to weight loss, improvement in mental health and quality of life was also observed. [41]

GLP-1 AGONISTS AND THE TREATMENT OF INSULIN RESISTANCE

GLP-1 is not active when blood glucose levels are normal or in the case of hypoglycemia. [42] GLP-1 analogs stimulate insulin secretion, decrease glucagon secretion, inhibit the hunger center, and delay gastric emptying, thereby improving postprandial glucose levels and inducing earlier satiety. They lower blood glucose levels without causing hypoglycemia and have a positive impact on patients with PCOS by reducing insulin resistance and improving metabolic changes. [43, 44] Obesity, a global pandemic, is a key component in the development of hyperinsulinemia, which plays a fundamental role in the pathomechanism of PCOS. Higher circulating insulin levels increase ovarian androgen production, which strongly influences PCOS symptoms. [45]

GLP-1 agonists positively affect insulin resistance in multiple ways. Possible mechanisms through which GLP-1 receptor agonists induce insulin sensitivity are illustrated in Figure 3. [45]

Effect	Mechanism
Increased insulin secretion	It increases the level of cAMP in the β cells signaling cascades involved in insulin secretion
Reducted oxidative stress	Improve the glycemic control Modulates oxidative phosphorylation
Decreased inflammatory responses	Reduces inflammatory mediators Reduces macrophage infiltration
Improved lipid profile	Modulates microRNA involved in lipid metabolism
Enhanced proliferation of islet β cells	Promotes Akt phospholyration and protein expression

Figure 3. Mechanisms of improved insulin sensitivity during using GLP-1 receptor agonists. [45]

In studies, the impact of GLP-1 receptor agonists on metabolic homeostasis was assessed. It was proven that all patients using liraglutide showed significant improvement in glycemic fluctuations during OGTT after 32 weeks of treatment compared to those in the placebo group. Fasting insulin sensitivity, as determined by the HOMA-IR method, also improved in the liraglutide group compared to the placebo therapy. Additionally, there was a sustained increase in the adjusted first-phase insulin secretion during liraglutide treatment and an improvement in β-cell function in patients with type 2 diabetes. [46]

GLP-1 improves fasting blood glucose levels through direct action on pancreatic islets and reduces postprandial hyperglycemia by inhibiting gastric emptying, which decreases the influx of glucose into the bloodstream. [47] Moreover, in obese patients, adipose tissue inflammation is a major driver of insulin resistance, and GLP-1 facilitates insulin sensitivity by reducing the inflammatory response. [45]

GLP-1 RECEPTOR AGONISTS AND HORMONES

PCOS is one of the leading causes of infertility in women, and its treatment focuses not only on improving metabolic parameters but also on regulating menstrual cycles. GLP-1 agonists can affect fertility in women with PCOS. [48] The GLP-1 receptor is distributed throughout the reproductive system, and observed effects in studies suggest that it may be an important modulatory signal linking the reproductive and metabolic systems, playing a stimulating role in reproduction. Data from clinical trials indicate improved menstrual regularity and increased fertility in overweight and/or obese women with PCOS treated with GLP-1 receptor analogs in the preconception period. [49] Treatment with liraglutide causes a significant reduction in free androgen levels compared to placebo. [49] Improvement in ovulation and hormonal regulation increases the chances of natural conception in women with PCOS.

SIDE EFFECTS AND SAFETY OF GLP-1 RECEPTOR AGONISTS

Adverse effects of GLP-1 receptor agonists can be inconvenient at the beginning of treatment. The most common are gastrointestinal complaints including nausea, vomiting, diarrhoea and abdominal discomfort. [26, 37] These may decrease over time, and they are related to the serum level of the medication. [50] Adverse effects such as hypoglycaemia, injection-site reactions, pancreatitis, neoplasia and gallbladder diseases are considered rare. Some studies showed the possibility of increased risk of thyroid C-cell tumours in patients using GLP-1 receptor agonists. Before starting treatment, the patient should be screened for contraindications such as history of pancreatitis, diabetic retinopathy, medullary thyroid cancer. Caution should also be applied to users of renin-angiotensin system inhibitors due to increased risk of acute kidney injury. [37]

THE COMPARISON OF GLP-1 RECEPTOR AGONISTS WITH METFORMIN

Metformin is a first-line treatment for women with PCOS and Diabetes Mellitus type 2 (DM2) or impaired glucose tolerance in whom lifestyle modification has been insufficient. [37] It has pleiotropic effects on glucose metabolism. Its main mechanism of action is inhibition of hepatic gluconeogenesis. In addition, it affects intestinal glucose absorption and increases insulin sensitivity. [26, 51, 52] It also has a number of actions particularly beneficial in patients with PCOS such as improving menstruation, hyperinsulinemia, hyperandrogenism and metabolic

disorders. Moreover, it has a preventive effect on cardiovascular events. [53] The undoubted advantage of metformin is that it has no hypoglycaemic effect and does not increase serum insulin levels. [52] GLP-1 receptor agonists are also safe while taking risk of hypoglycaemia into consideration. [54] Their mechanism of action involves glucose-dependent release of insulin from the pancreatic islets, delayed gastric emptying, inhibiting the production of glucagon as well as satiety enhancement. [37]

Yi Han et al. conducted a meta-analysis that showed a superiority of GLP-1 receptor agonists over metformin in terms of increasing insulin sensitivity, reducing body mass index (BMI) and abdominal obesity in women with PCOS. There was no statistically significant difference between GLP-1 receptor agonists and metformin in terms of menstrual frequency, serum total testosterone, free androgen index (FAI), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEA-S), Ferriman-Gallwey scores, androstenedione, LH, fasting blood glucose (FBG), fasting insulin (FINS), triglycerides, total cholesterol and blood pressure. Side effects like headache and nausea were more common with GLP-1 receptor agonists than with metformin. [50]

The advantage of metformin compared to GLP-1 receptor agonists is the oral route of administration. It enables to avoid patient discomfort and increases adherence. Currently, there is only one GLP-1 receptor agonist administered orally available on the market – semaglutide. [55]

COMBINATION THERAPY WITH METFORMIN AND GLP-1 RECEPTOR AGONISTS

GLP-1 receptor agonists can be used both in monotherapy and in combination with insulin sensitizers such as metformin. [37] The study showed the superiority of combination (Metfromin + Exenatide) over monotherapy with one of these medications. Menstrual cycle regularity as well as endocrine and metabolic disorders were all improved. Weight reduction may be partly responsible for the improvement in fertility, insulin-glucose parameters and adiponectin levels in the patients. [56]

IMPACT OF GLP-1 RECEPTOR AGONISTS ON THE LIVER

Patients struggling with PCOS have mitochondrial dysfunction and elevated serum androgen levels. This may explain the increased prevalence of Non-alcoholic Fatty Liver Disease

(NAFLD) in these patients. [37] It is suggested that therapy with GLP-1 receptor agonists may have beneficial effects on liver function. [37] H. Kahal and colleagues conducted a study showing that weight reduction combined with liraglutide therapy significantly reduced liver fibrosis index levels in obese women with PCOS. These finding prompts consideration of this therapy in women with PCOS, obesity and NAFLD. [57] It has also been shown that the prevalence of NAFLD was reduced in approximately 68% of patients who received liraglutide therapy. [58] In addition, studies are underway to investigate the efficacy of GLP-1 receptor agonists in the treatment of non-alcoholic steatohepatitis (NASH). [37]

CONCLUSIONS

PCOS is an endocrinopathy affecting many young women. Although the first visible symptom of this disease is obesity, it is not just a cosmetic defect. PCOS is associated with a variety of other pathophysiological processes in the body, such as hyperandrogenemia, insulin resistance, hyperinsulinemia, dyslipidaemia and impaired fertility. This can lead to many life- threatening complications like increased risk of cardiovascular events or endometrial hyperplasia and cancer. That is why it is so important to introduce treatment promptly in PCOS patients. It is possible to start with lifestyle modification. However, this action often does not have significant effects, and pharmacotherapy is recommended as a second step. Metformin is commonly used for treatment. Despite improving insulin sensitivity, normalizing glucose level, preventing type 2 diabetes, regulating menstrual cycles and reducing androgen levels, it shows moderate effects on weight reduction. GLP-1 receptor agonists are medications showing superiority in terms of improving insulin sensitivity, reducing BMI and abdominal obesity which also results in improvement of fertility. They indicate cardioprotective effects and enhance liver function in obese women with PCOS. In addition, they are considered safe medicines with a low rate of life-threatening side effects, making them a valuable therapeutic option to consider in obese women with PCOS.

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