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Abstract

Polycystic ovary syndrome is a prevalent issue in women's health that is associated with hyperinsulinemia and insulin resistance and can lead to long-term health problems. The most highly recommended treatments are diet and lifestyle changes. If these changes alone are not enough, pharmacologic treatments may be employed, which include metformin, spironolactone or thiazolidinediones, although more research is needed to fully realize their role. The role of the pharmacist in this disease state includes counseling patients on healthy lifestyle changes, consulting with the physician about prescribing the best medication for each patient, and monitoring therapy adherence in the patient.

Introduction

Polycystic ovarian syndrome (PCOS) is a prevalent disorder affecting 6-15 percent of women of reproductive age.¹ PCOS is a pleiotropic syndrome that can have deleterious effects on the entire body. Hyperinsulinemia is one of the main concerns associated with this syndrome because it can increase the risk for many other disease states in a woman with PCOS. There are few treatment options for PCOS at this time; but by understanding the safety and efficacy of the available options, pharmacists can help their patients better understand the disease state and medications. Pharmacists can further take an active role by providing screenings and educating patients on preventative measures for women who are at risk of developing this disease.

PCOS

Polycystic ovarian syndrome is the most common endocrine disorder among premenopausal women.¹ The symptoms of this disorder are varied and extend beyond reproductive system problems. Along with menstrual irregularities, chronic anovulation and possible infertility, women with PCOS often develop hirsutism, acne, hyperandrogenism and inappropriate gonadotropin secretion.^{1,4} While some of the symptoms may only be frustrating or uncomfortable for the patient, a woman with PCOS is at risk for developing other conditions that are not as benign. A PCOS diagnosis means the patient is at an increased risk for insulin resistance, hyperinsulinemia, dyslipidemia, hypertension, gestational and type 2 diabetes, systemic inflammation, endothelial dysfunction, and cardiac events such as myocardial infarction or cerebral vascular accident.⁵ Although PCOS is a common problem, its pathogenesis remains unknown. It is not merely a structural disorder; rather, it has definite ties to problems with hormones, genetics, and even potentially altered central nervous system (CNS) function.⁶ There are theories that PCOS has a genetic component due to a gene mutation in ovarian and adrenal androgen synthesis as evidenced by a higher incidence of PCOS among first-degree relatives. CNS problems such as epilepsy and bipolar disorder may also play a role in PCOS but more research needs to be done before a more concrete conclusion is reached regarding this potential relationship.

Hyperinsulinemia

Hyperinsulinemia and insulin resistance are commonly associated with PCOS. Hyperinsulinemia increases production of already elevated androgens, worsening PCOS symptoms. This is accomplished by overproduction of ovarian androstenedione and adrenal dehydroepiandrosterone (DHEA), which leads to excess estrogen in the periphery. Elevated estrogen increases the ratio of luteinizing hormone (LH) secreted by the anterior pituitary gland to secretion of follicle stimulating hormone (FSH).¹ Increased LH secretions lead to amenorrhea, infertility, anovulation and hyperandrogenism.

The hypothalamic-pituitary axis also is affected by excess release of adrenocorticotropic hormone (ACTH) in response to corticotropin-releasing hormone (CRH).¹ ACTH stimulates lipoprotein uptake by cortical cells, which can lead to higher cholesterol levels. This dysregulation of cholesterol levels correlates to the finding that many women with PCOS are obese. Hyperinsulinemia also may possibly contribute to this weight gain. Overall, insulin resistance and compensatory hyperinsulinemia are contributing factors for anovulation, hyperandrogenism, infertility and early pregnancy loss associated with PCOS patients (Figure 1).

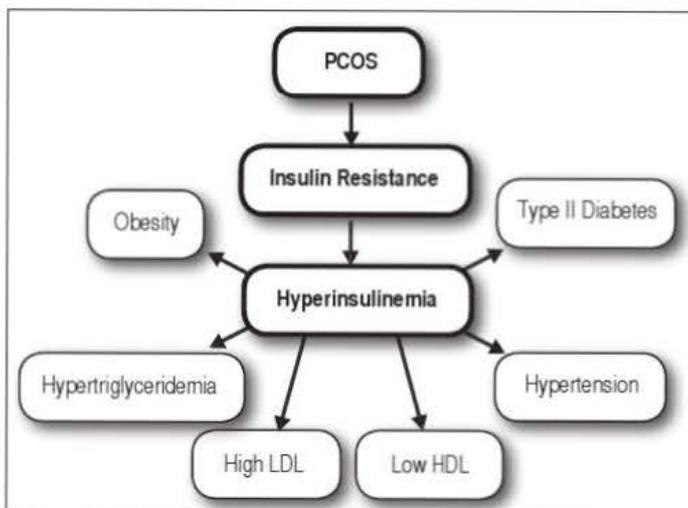


Figure 1. Detrimental effects of PCOS-induced hyperinsulinemia

Non-pharmacologic Treatment Options

The most highly recommended way to treat PCOS is altering the diet to include healthier options, such as whole grains and fresh produce, and reduce the intake of highly processed foods and foods high in fat or sodium. Incorporating exercise into daily life also is recommended.⁷ Eating foods that help decrease LDLs and increase HDLs, such as high fiber foods and foods containing omega-3 fatty acids (fish and nuts), can be beneficial dietary modifications.⁸ Achieving ideal body weight and exercising at least five times per week can potentially alleviate many symptoms associated with PCOS as well as reverse the progression of concurrent disease states.

A diet that has recently received significant media and patient attention is the human chorionic gonadotropin (hCG) diet. Human chorionic gonadotropin is a hormone produced by the trophoblastic cells of the placenta during pregnancy.⁹ The hCG diet supposedly mobilizes fat stored in the abdomen, hips and thighs while keeping the patient feeling satiated. The diet involves three "gorging days," to build up calories in the body, followed by a strict, very low-calorie diet of 500 calories a day while receiving hCG as injections, sublingual drops or lozenges. Despite some clinical trials showing benefits, the FDA denies that hCG has any benefit in treating obesity.¹⁰ Currently, the only FDA-approved use for hCG is for fertility treatment.¹¹ The diet is not recommended for weight loss in most patients, but it may be used as a last resort for patients who desperately need to lose weight. Pharmacists can counsel patients about the risks associated with the diet, monitor its correct use and ensure the safety of the patients.

Pharmacologic Treatment Options

There are limited pharmaceutical options that can be utilized; however, because of the underlying problem with hyperinsulinemia, insulin-sensitizing agents may be beneficial in treating PCOS.¹² The three products that currently are used in the treatment of PCOS are metformin, spironolactone and thiazolidinediones (TZDs). These medications all have different mechanisms of action and treat PCOS in a variety of ways. Further research is necessary prior to widespread use of these agents.

Metformin is a commonly used and studied treatment of PCOS in patients with hyperinsulinemia. There are various potential mechanisms by which metformin may lower insulin levels, including the inhibition of gluconeogenic enzymes, reduced uptake of enzymes needed for hepatic gluconeogenesis, increased phosphorylation of insulin receptor and insulin receptor substrates, and inhibition of mitochondrial respiration, which can reduce the energy supply needed for gluconeogenesis.¹³ In patients with PCOS, the lowering of insulin levels can lead to improved ovarian function as well as improved glucose metabolism.¹⁴ Lowering insulin levels also may reverse the dysfunction in the hypothalamic-pituitary-ovarian axis, causing a decrease in androgen levels.¹³ Additionally, metformin has effects on free fatty acid synthesis, which indirectly lowers gluconeogenesis activity. It does this through antagonism of acetyl-CoA carboxylase activity so that there is decreased fatty acid synthesis and increased mitochondrial fatty acid oxidation. These two effects on the body lead to a reduction in hepatic lipid levels and lowered plasma triglyceride levels. While the effects of metformin seem to be beneficial in women with PCOS, there are side effects to consider that may deter patient use of this medication. The most common issues are gastrointestinal-related, such as nausea, vomiting and diarrhea.¹⁵ These are typically resolved in a few days or weeks and can be minimized by taking metformin with meals and following a gradual titration schedule.¹³ A change in diet and exercise patterns, along with the use of metformin, can improve cardiometabolic irregularities and may even restore ovarian function.

Spironolactone is another treatment option for women with PCOS. Along with diuretic properties, spironolactone may be used as an antiandrogen for female hirsutism. Though the mechanism is unknown, it is thought to block androgen receptors and may decrease the overall production.³ According to a randomized, open-label study of 69 PCOS patients comparing spironolactone and metformin treatment, there was no significant effect on BMI, waist-to-hip ratio, blood pressure, oral glucose tolerance

test parameters or insulin sensitivity when patients received a 50 mg/day dose of spironolactone.¹⁶ However, there was a significant improvement in menstruation cycle, hirsutism and androgen levels. While spironolactone was superior in helping with hirsutism and patient acceptance, metformin was more effective at improving glucose tolerance and insulin sensitivity. Although spironolactone is an option in the treatment of PCOS, it is not preferred because it does not cause significant improvement in glucose tolerance and insulin sensitivity.

Another pharmacologic option is a TZD such as rosiglitazone or pioglitazone. Both of these drugs are agonists of the peroxisome-proliferator-activated receptors (PPARs), which, when activated, influence the production of proteins involved in glucose and lipid metabolism.¹⁵ This improves response to insulin without influencing the amount of insulin that is secreted by the pancreas. In a randomized, two-armed, head-to-head study of 96 patients, it was found that rosiglitazone was more effective than metformin at reducing female hirsutism, but it was not found to be more beneficial at reducing insulin levels, even though there was a significant reduction in fasting insulin levels in the use of rosiglitazone.² Although these results sound promising, due to a recent change in the FDA Black Box Warning regarding increased risk of cardiac events, rosiglitazone should not be used in PCOS patients because they are predisposed to such events.

Pioglitazone has also been studied in the treatment of PCOS. A randomized controlled trial of 52 patients found that a six-month administration of pioglitazone in obese women was as effective as metformin in reducing fasting insulin levels without drastically changing glucose concentration.¹⁷ There also was a significant reduction in hirsutism and serum concentrations of testosterone and androgens. Pioglitazone use may cause an increased risk of bladder cancer as indicated by the FDA Black Box Warning. This risk should be taken into consideration when choosing a treatment, and patients should be monitored. Due to the Black Box warnings, and because there's no significant benefit over metformin or spironolactone, the use of TZDs in women with PCOS is not recommended as a first choice of therapy in the treatment of PCOS.

Conclusion

Pharmacists can assume an active role when assisting with the treatment of hyperinsulinemia in PCOS. Awareness of the treatment options available can allow pharmacists to ensure that prescribers are utilizing the optimum treatment plan for the patient. Metformin is generally the first-choice option in the treatment of hyperinsulinemia in PCOS. Since there are several negative side effects associated with the drug, the pharmacist can communicate with the prescriber about a titration schedule in order to make the patient more comfortable. Spironolactone is not as effective as metformin in treating hyperinsulinemia, but it does treat the problems caused by excess androgens. TZDs are not recommended in the treatment of PCOS because of the Black Box warnings and concerns of patient safety; however, patients already taking a TZD should be counseled on correct and safe use. Aside from counseling the patients on their prescribed medications, pharmacists can help with screenings to track patient progress. Such screenings include glucose screenings, lipid panel screenings, and body mass index values. Becoming involved in the outpatient setting can allow pharmacists to alert patients to any concerning lab values or assist patients with plans and

tracking of lifestyle changes. Because of the complexity of PCOS, it is important to treat each patient based on individual symptoms and needs. Due to the accessibility of pharmacists, counseling PCOS patients is a positive opportunity to take on an integral role in helping patients manage and improve the symptoms of this disease state.

References

1. Romualdi D, Giuliani M, Draisci G, Costantini B, Cristello F, Lanzone A, Guido M. Pioglitazone reduces the adrenal androgen response to corticotropin-releasing factor without changes in ACTH release in hyperinsulinemic women with polycystic ovary syndrome. *Fertil Steril*. 2007; 88(1): 131-138.
2. Yilmaz M, Karakoc A, Toruner FB, Cakir N, Tiras B, Ayvaz G, Arslan M. The effects of rosiglitazone and metformin on menstrual cyclicity and hirsutism in polycystic ovary syndrome. *Gynecol Endocrinol*. 2005; 21(3): 154-160.
3. Bhatia V. Insulin resistance in polycystic ovarian disease. *Southern Medical Association*. 2005; 98(9):902-909.
4. Fulghesu AM, Ciampelli M, Guido M, Murgia F, Caruso A, Mancuso S, Lanzone A. Role of opioid tone in the pathophysiology of hyperinsulinemia and insulin resistance in polycystic ovarian disease. *Metabolism*. 1998; 47: 158-162.
5. Banaszewska B, Pawelczyk L, Spaczynski RZ, Duleba AJ. Comparison of simvastatin and metformin in treatment of polycystic ovary syndrome: prospective randomized trial. *J Clin Endocrinol Metab*. 2009; 94(12): 4938-4945.
6. Abbott Laboratories. *Understanding Obesity and Polycystic Ovary Syndrome*. 2006. Abbott Park, IL.
7. Insulin Resistance and Hyperinsulinemia. Jewish Hospital Cincinnati, Catholic Healthcare Partners. 2010. Available at www.jewish-hospitalcincinnati.com/cholesterol/Research/insulin_resistance.html. Accessed Oct. 29, 2010.
8. HDL cholesterol: How to boost your "good" cholesterol. Mayo Foundation for Medical Education and Research. 2010. Available at www.mayoclinic.com/health/hdl-cholesterol/CL00030/NSECTIONGROUP=2. Accessed Oct. 29, 2010.
9. Belluscio DO, Ripamonte L, and Wolansky M. Utility of an Oral Presentation of hCG (Human Chorionadotropin) for the Management of Obesity: A Double Blind Study. *The Original Internist*. 2009: 197-211.
10. Robb-Nicholson C. By the Way, Doctor: I've been trying to lose weight for a long time and nothing seems to work. What do you know about the HCG diet? *Harv Womens Health Watch*. 2010; 17:8.
11. Scheve T. How the HCG Diet Works. Discovery Communications Inc. 2010. Available at health.howstuffworks.com/wellness/diet-fitness/weight-loss/hcg-diet3.htm. Accessed Oct. 29, 2010.
12. Cheang KI, Sharma ST, Nestler JE. Is Metformin a primary ovulatory agent in patients with polycystic ovary syndrome? *Gynecol Endocrinol*. 2006; 22(11):595-604.
13. Diamanti-Kandarakis E, Economou F, Palimeri S, Christakou C. Metformin in polycystic ovary syndrome. *Ann NY Acad Sci*. 2010; 1205: 192-198.
14. Sahin I, Serter R, Karakurt F, Demirbas B, Culha C, Taskapan C, Kosar F, Aral Y. Metformin versus flutamide in the treatment of metabolic consequences of non-obese young women with polycystic ovary syndrome: a randomized prospective study. *Gynecol Endocrinol*. 2004; 19: 115-124.
15. Lexi-Comp [database online]. Hudson, OH: Lexi-Comp, Inc. 2010. Available at online.lexi.com/crlsqli/servlet/crlonline. Accessed Oct. 29, 2010.
16. Ganie MA, Khurana ML, Eunice M, Gupta N, Gulati M, Dwivedi SN, Ammini AC. Comparison of efficacy of spironolactone with metformin in the management of polycystic ovary syndrome: an open-labeled study. *J Clin Endocrinol Metab*. 2004; 89(6):2756-2762.
17. Ortega-González C, Luna S, Hernández L, Crespo G, Aguayo P, Arteaga-Troncoso G, Parra A. Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2005; 90(3): 1360-1365.