Natural Approaches for Treating Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) is a complex medical condition involving multiple body systems. The etiology of this condition is unknown. In addition, there is currently no consensus on the diagnostic criteria for PCOS. It is accepted that hyperandrogenism, insulin resistance, and menstrual abnormalities are commonly present. An estimated 6–10 percent of reproductive-age women have PCOS, making it one of the most common endocrine reproductive disorders.[1]

Etiology

The cause of PCOS is unknown. Many studies have indicated that either insulin resistance or endocrine dysfunction can cause the symptoms associated with this condition.[2] Many theories have been suggested to explain the primary defect that causes PCOS pathology. They include abnormal insulin action and secretion, endocrine abnormalities causing an increased luteinizing hormone (LH) pulse frequency and amplitude, increased androgen production from the ovaries, and abnormal cortisol metabolism.[2] There is also evidence that genetic factors play a role in PCOS.[3] Eating disorders, such as bulimia and binge eating, have been also been associated with this condition.[4]

Symptoms

PCOS involves metabolic, endocrine, and clinical manifestations. Studies have suggested that 75–80 percent of women with PCOS have irregular menstrual cycles. These women typically have 5–9 menstrual cycles per year, ranging from 40–65 days in length. Increased androgens cause hirsutism in 60–80 percent—as well as alopecia in 40–70 percent—of these women. Acne is also increased and prevalent in 40–60 percent of women with PCOS.

Obesity is common in this condition and studies have suggested that 75 percent of women with PCOS are overweight or obese.[5] These women often have increased abdominal adiposity with an average waist-to-hip ratio of 0.86.[6] Of these overweight women, an estimated 10 percent have *acanthosis nigricans*, commonly found in the axilla, nape of the neck, and skin folds. Increased prolactin can also cause breast discharge in 8–10 percent of affected women. Finally, sleep apnea may also occur in approximately 8 percent of women with PCOS.[5] Other endocrine diseases with similar symptoms must be ruled out in order to diagnose PCOS.

Pathophysiology

Insulin Resistance

Insulin resistance can be caused by increased peripheral insulin resistance of the target tissue, increased pancreatic sensitivity, or decreased hepatic clearance. Studies have shown that insulin resistance and hyperinsulinemia are common in women with PCOS. In addition, obese women with PCOS have had decreased insulin sensitivity compared to lean women with the condition.[7] However, some studies have not found abnormal insulin action in lean women with PCOS.[8]

Pancreatic beta-cell dysfunction similar to that of type 2 diabetes has also been found in women with this condition.[9] In addition, studies have shown an increase in serine phosphorylation at the insulin receptor causing an inhibition of signaling. Serine phosphorylation of insulin-receptor substrate-1 is also associated with the tumor necrosis factor–α-mediated insulin resistance seen with obesity. It is also important that serine phosphorylation increases the activity of the enzyme P450c17 in adrenal and ovarian tissue. This enzyme is a key regulatory molecule in androgen synthesis, and serine phosphorylation has been shown to increase androgen synthesis. Research has indicated that serine phosphorylation causes insulin resistance in at least 50 percent of women with PCOS.[10]

Hyperandrogenism

Although studies have yielded conflicting results, current evidence suggests that the hyperinsulinemia causes the hyperandrogenism seen in women with PCOS. Studies have indicated that insulin increases the amplitude of the LH pulse in obese women with PCOS.[11] In addition, insulin decreases the synthesis of sex–hormone binding globulin (SHBG) from the liver, which increases the bioavailability of androgens.

Insulin also decreases the production of insulin growth factor (IGF) binding protein–1 (IGFBP-1) in the liver and the ovaries, which causes an increase in available IGF-1.[12] Studies have shown that insulin and IGF-1 increase thecal androgen response to LH[13] and that high levels of insulin can bind the IGF receptor leading to an increase in androgen production.

Nutrient and Herbal Interventions for Polycystic Ovary Syndrome

Nutrient	Dose
Research strongly supports these interventions	
Vitamin C	400–2000 mg/day
Chromium picolinate	400 mcg/day
D-chiro-inositol	600 mg/day
N-acetyl-cysteine	1.2 g/day
Some research supports these interventions	
Stinging nettle (*Urtica dioica*)	300–900 mg/day
Zinc	25–50 mg/day
Momordica (bitter melon; *Momordica charantia*)	900–1800 mg/day
Alpha lipoic acid	600 mg/day
Clinical or historical use supports these interventions	
Soy (*Glycine* spp.) protein extract	20–40 g/day
Gymnema (Gymnema sylvestre)	400 mg/day
Essential fatty acids	1–3 g/day
Saw palmetto (*Serenoa repens*)	320 mg/day

Diabetes and Glucose Intolerance

Interestingly, studies have shown that 82 percent of women with type 2 diabetes had polycystic ovaries (shown via ultrasound tests). Yet, only 52 percent of these women had symptoms of hyperandrogenism or menstrual abnormalities. Thus, it is clear that insulin resistance is only one factor causing PCOS. Studies have indicated that glucose intolerance is found in 31 percent of patients with PCOS and type 2 diabetes is found in 7.5 percent of obese women with PCOS.

Approximately 10 percent of nonobese women with PCOS have glucose intolerance, and 1.5 percent of these women have type 2 diabetes.[9] In addition, women with PCOS have a fivefold-to-tenfold rate increase in converting from glucose intolerance to type 2 diabetes.[14]

Cardiovascular Disease

There is an increased risk of cardiovascular disease (CVD) among women with PCOS. Studies have shown that, although atherosclerosis is not specifically increased in women with PCOS, carotid artery *intima media* thickness is increased significantly in these women, suggesting subclinical atherosclerotic changes.[15]

In addition, hyperandrogenic insulin-resistant women with PCOS have abnormal endothelial function. Endothelin-1 (ET-1) is a potent vasoconstrictor molecule that has been shown to be elevated in women with PCOS regardless of obesity, which appears to be indicative of abnormal vascular reactivity, endothelial injury, and increased risk for CVD.[16]

Women with PCOS have increased risk for abnormal lipid levels as well. Studies have shown increases in triglycerides and low-density lipoprotein cholesterol, and decreased high-density lipoprotein cholesterol.[17] Women with PCOS have also been shown to have increased levels of plasminogen activator inhibitor (PAI-1).[18] Insulin resistance and increased risk of thrombotic vascular events is associated with increased PAI-1.[19]

Endocrine Abnormalities

Many endocrine abnormalities are seen in PCOS. One significant finding is the increase in LH surge amplitude and frequency seen in approximately one third of women with this condition.[20] Follicule-stimulating hormone (FSH) levels are usually normal or low.

The LH diurnal secretion pattern is also abnormal, peaking in late afternoon instead of at night. Gonadotropin-releasing hormone (GnRH) secretion is also atypical in these women. GnRH is secreted in a rapid pulse frequency that increases LH synthesis, increases androgens, and inhibits the maturation of follicles.[21] Progesterone supplementation to anovulatory women with PCOS also causes a slower GnRH pulse frequency and increased FSH secretion and follicle maturation.[21]

In addition, it has been shown that the hypothalamus GnRH pulse generator is less sensitive to inhibition by estradiol and progesterone in women with this condition, requiring higher levels to decrease the pulse frequency than controls.[22]

Ovarian Abnormalities

Studies have suggested that women with PCOS may have increased 17α-hydroxyprogesterone and androstenedione as a result of abnormal enzyme regulation in the ovaries. In vitro studies of thecal cells from polycystic ovaries show that androstenedione production per cell is increased with or without LH stimulation compared to normal thecal cells.[23] Additional studies have shown an abnormal steroid synthesis in the ovaries, possibly caused by the ovarian P450c17 enzyme, which is a key enzyme in the biosynthesis of androgens.

Researchers have also investigated abnormalities in the 17β-hydroxysteroid dehydrogenase (17βHSD) isoenzymes, which are involved in testosterone synthesis and also found in the ovaries. This research showed an increase of P450c17 activity by 500 percent and 3βHSD by 1000 percent in thecal cells from polycystic ovaries, although 17βHSD activity was the same compared to cells from control ovaries.[24]

Decreasing insulin levels and weight loss causes a decrease in the activity of the P450c17 enzyme and decreases testosterone levels in obese and in nonobese women with PCOS.[25]

Adrenal Abnormalities

Adrenal androgen synthesis is increased in 26 percent of women who have symptoms consistent with PCOS.[26] Studies have shown an increase in 5α-reductase activity in women with PCOS, which could cause an inactivation of cortisol. The enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which converts cortisone to cortisol, is also abnormal in women with this condition.[27]

These enzyme abnormalities would lead to an increase in adrenocorticotropic hormone secretion to maintain normal cortisol levels and thus, an increase in adrenal androgen production.

Also, total cortisol metabolites measured in the urine have been found to be higher in women with PCOS.[28]

Genetics and Prenatal Exposure

Studies have shown that first-degree relatives of women with PCOS have an increased incidence of this condition. Research has demonstrated that 40 percent of women with PCOS have sisters with the condition and that 35 percent have mothers with PCOS.[3] A twin study done on women with PCOS showed that androgen levels, insulin levels, and body–mass (BMI) were influenced genetically, and the researchers proposed that PCOS is possibly X-linked or influenced by polygenic factors.[29]

More specifically, evidence has shown that PCOS is linked to polymorphism of the regulatory region CYP11a, which codes for an important enzyme in the steroidogenic pathway. PCOS has also been associated with the class III allele in a satellite regulation region of the insulin gene called the INS-VNTR.[30]

Some research indicates that women with PCOS have an increased incidence of uterine cancer.

Studies with Rhesus monkeys have demonstrated that intrauterine exposure to increased androgens can cause the symptoms associated with PCOS in adults, such as hyperandrogenism, insulin resistance, increased LH levels, and anovulation.[31] Human studies suggest that obese women with PCOS have increased ovarian secretion of androgens and have increased birth weight and maternal obesity, while thin women with PCOS have abnormal LH secretion as a result of prolonged gestation.[32]

Cancer

Chronic anovulation, obesity, and hyperinsulinemia are all associated with both PCOS and endometrial carcinoma. Anovulatory menstrual cycles cause increased levels of unopposed estrogen, which, in turn, can lead to endometrial hyperplasia and possibly to endometrial cancer. Although there are some studies with conflicting results, some research indicates that women with PCOS have an increased incidence of uterine cancer.[33] In addition, most young women with uterine cancer have PCOS.[34] Studies showing that women with PCOS have a threefold increased incidence of breast cancer are controversial.[35]

Diagnosis

Currently, there is no consensus on the diagnostic criteria for PCOS. It is generally accepted that oligo-ovulation and hyperandrogenism are present and other diseases with similar symptoms have been excluded.

Polycystic ovaries found on transvaginal ultrasound are present in only approximately 80–90 percent of women with PCOS.[36] Polycystic ovaries are also found in many women without any symptoms of PCOS; thus, this finding is associated with the condition but is not considered to be diagnostic. Ultrasound criteria for PCOS are variable; however, generally the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter or an increased ovarian volume (>10 mL) is correlated with a diagnosis of PCOS.[37]

Women with PCOS have inappropriate gonadatropin secretion. Increases in LH, abnormal LH pulse frequencies, and elevated LH-to-FSH ratios are frequently seen.[2] However, LH levels are suppressed with increasing BMI and obesity, making it less useful as a diagnostic tool.

Elevated circulating total testosterone or free testosterone levels have been the most useful hormone indicators that can be tested to correlate with PCOS. Testing for insulin resistance is done initially with fasting glucose and insulin levels. However, an oral glucose tolerance test is frequently necessary because normal fasting insulin levels can be found in type 2 diabetes caused by beta-cell failure. Studies have indicated that approximately 40 percent of women with PCOS are glucose-intolerant.[38] Conditions with similar presentation that need to be ruled out include Cushing's disease, adrenal 21-hydroxylase deficiency, hyperprolactinemia, and androgen-producing tumors.

Conventional Treatments

Conventional medical treatment involves a number of pharmaceuticals because of the many body systems affected by the condition, which causes a vast array of symptoms.

Metformin

Metformin hydrochloride is commonly prescribed to treat insulin resistance and glucose intolerance. This drug reduces fasting glucose levels and improves oral glucose tolerance in patients with type 2 diabetes, possibly by reducing glucose output from the liver. Studies performed on women with PCOS showed that metformin not only improved glucose tolerance but also reduced total testosterone and free testosterone, and increased the levels of SHBG.[39]

However, conflicting results in similar studies demonstrated that weight and obesity also play roles in the effectiveness of metformin.[40] A study on women with PCOS and oligo-ovulation showed that that treatment with metformin caused 23 percent of the patients to ovulate.[41]

When metformin was combined with clomiphene citrate, the ovulation rate jumped to nearly 90 percent compared to 12 percent of women who took placebo.[42] Continuing metformin while pregnant has also been shown to decrease the rate of spontaneous abortions in women with PCOS.[43] Metformin treatment may also provide cardiovascular benefits as studies have indicated that the drug decreases ET-1, PAI-1, and lipoprotein(a).[16,44]

Estrogen–Progestin Combinations

Oral contraceptives are commonly used to treat symptoms associated with hyperandrogenism, such as acne, hirsutism, and hair loss. An estrogen–progestin combination suppresses LH,

which, in turn, decreases androgen levels and increases SHBG levels. Increasing SHBG decreases the amount of bioavailable testosterone. Estrogen also suppresses sebaceous cell function directly. The form of progestin is an important consideration because some forms are more androgenic than others. Desogestrel and norgestimate are both low androgenic forms of estrogen and are commonly used for women with PCOS.[45]

Antiandrogens

Antiandrogens, such as spironolactone, are used to treat symptoms such as acne and hirsutism. This drug can cause menstrual abnormalities; thus, it is commonly used in conjunction with oral contraceptives. Other antimineral corticoids, such as flutamine and cyproterone acetate (not available in the United States), have been effective for treating symptoms associated with androgen excess.[45]

GnRH agonists

GnRH agonists, such as leuprolide, are used to suppress the pituitary–ovarian axis. This causes a decrease in ovarian secretion of estrogen and androgens. This drug is usually used for short periods of time because of the bone loss associated with hypoestrogenism.

Eflornithine

Eflornithine is a topical treatment for hirsutism. It inhibits the enzyme ornithine decarboxylase in the skin. This causes a decrease in the rate of hair growth.

Clomiphene

Clomiphine citrate is an antiestrogen used to increase LH and FSH to induce ovulation for enhancing fertility. Studies have shown that this agent can induce ovulation in approximately 80 percent of oligo-ovulatory women.[46]

Nutrients and Herbal Interventions

Several herbal and nutrient interventions are recommended because of the complexity of this condition. Some therapies can improve ovulation and insulin sensitivity and reduce hyperandrogenism.

Chromium

Chromium is a trace element commonly used for blood-sugar balancing. Chromium in the trivalent form is found in many foods such as whole-grain products, egg yolks, coffee, nuts, brewer's yeast, meat, green beans, and broccoli.

Chromium deficiency often presents with impaired glucose, insulin, and lipid metabolism. Research has demonstrated that chromium supplementation reduces glucose intolerance and relieves symptoms of type 1 and type 2 diabetes, as well as those of gestational diabetes.[47]

The proposed mechanism of action for the insulin response to chromium is focused on the insulin receptor. Chromium activates the insulin receptor kinase and inhibits the insulin receptor phosphotyrosine phosphatase enzyme. This causes increased phosphorylation of the insulin receptor and increased insulin sensitivity and may facilitate glucose transport into cells.[48] In addition, chromium may augment insulin binding, insulin receptor number, and beta-cell sensitivity.[49] A study performed on women with PCOS showed that chromium supplementation improved glucose tolerance in this population.[50]

Vitamin C

Vitamin C has multiple functions including antioxidant and collagen-stimulating properties. A study performed on anovulatory women for whom clomiphene failed showed that oral supplementation with vitamin C (400 mg per day) increased ovulation both with and without clomiphene citrate.[51] In addition, a study indicated that vitamin C supplementation for infertile women with luteal-phase defects may increase progesterone levels.[52] Vitamin C has also been shown to improve endothelial-dependent vasodilation, which has been shown to be abnormal in women with PCOS.[53]

N-Acetyl-Cysteine

N-acetyl cysteine (NAC) is a derivative of the amino acid L-cysteine. NAC is the precursor to glutathione and is commonly used for its antioxidant, anti-inflammatory, and mucolytic actions. A study performed on women with PCOS whose conditions are resistant to clomiphene showed that NAC supplementation of 1.2 g per day plus clomiphene significantly increased ovulation and pregnancy rates.[54]

Zinc

Zinc is an essential trace mineral and is a required cofactor for numerous biochemical reactions. Zinc has been shown to affect glucose transport and insulin levels. Evidence suggests that zinc supplementation can improve glucose tolerance and increase insulin-induced glucose transport into cells.[55] In addition, some research indicates that zinc may be deficient in individuals with type 2 diabetes.[56]

Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) is a coenzyme used in carbohydrate metabolism and adenotriphosphate (ATP) production, and is a potent free-radical scavenger. ALA has been shown to improve insulin sensitivity, and several studies on patients with type 2 diabetes have demonstrated that ALA supplementation increases metabolic clearance of glucose by as much as 50 percent.[57]

ALA supplementation can also increase glucose uptake into skeletal muscle by 40–300 percent.[58] Research has demonstrated that ALA stimulates adenosine monophosphate–activated protein kinase in skeletal muscle, which causes a decrease in triglyceride accumulation. Studies have suggested that triglyceride accumulation in skeletal muscle contributes to insulin resistance.[59]

Essential Fatty Acids

Essential fatty acids cannot be made by the body and thus need to be consumed in the diet. Omega-3 fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and omega-6 fatty acids such as gamma-linolenic acid (GLA) are

often taken as supplements because of their strong anti-inflammatory action.

EPA and DHA are present in high amounts in fish oils and produce anti-inflammatory and antithrombotic effects. Specifically, EPA has cardioprotective effects, such as decreasing triglycerides and increasing high-density lipoprotein (HDL).[60] As previously mentioned, women with PCOS often have hyperlipidemia with elevated triglyceride levels and low HDL levels.

Stinging nettle (*Urtica dioica*).

Saw palmetto (*Serenoa repens*).

EPA and DHA decrease inflammatory eicosanoids by competing with arachidonic acid (AA) in the lipo-oxygenase and cyclo-oxygenase pathways. GLA is commonly found in borage (*Borago officinalis*) seed oil, evening primrose (*Oenothera* spp.) oil, and black currant (*Ribes nigrum*) oil. GLA decreases the inflammatory response by inhibiting the production of inflammatory leukotrienes from AA.[61]

Momordica

Momordica (*Momordica charantia*) fruit, commonly known as bitter melon, has historically been used to improve blood-sugar control. A study demonstrated that supplementation with bitter melon improved glucose tolerance in 73 percent of patients with diabetes who were treated with the supplement.[62] Another study also showed that treatment with bitter melon improved both fasting and 2-hour postprandial glucose levels in 86 percent of individuals with type 2 diabetes.[63]

Gymnema

Gymnema (*Gymnema sylvestre*) is a tropical plant used medicinally to treat hyperglycemia. Research has shown that gymnema supplementation decreases glucose levels in hyperglycemic rats. Other studies have shown that using this herb as a supplement decreases glucose absorption in the intestines, stimulates pancreatic beta-cell growth, and stimulates insulin release from beta cells.[64,65]

Stinging nettle

Medicinal use of stinging nettle (*Urtica dioica*) involves both the root and leaf of this plant. Studies have shown that the lignans in the root competitively bind SHBG. This binding may cause an increase in circulating SHBG providing a relative decrease in bioavailable androgens.[66]

Saw palmetto

Saw palmetto (*Serenoa repens*) is an herb commonly used, because of its antiandrogen and anti-inflammatory properties, for treating benign prostate hypertrophy (BPH). The lipid portion of the berries is used medicinally to produce these effects. Studies have shown that saw palmetto inhibits 5α-reductase in the prostate, which decreases conversion of testosterone to the more potent form dihydrotestosterone.[67] Although saw palmetto has not been studied as a PCOS treatment, the herb's antiandrogenic activity may be beneficial for patients with the condition.

Soy

Soy (*Glycine* spp.) protein extracts and isoflavones produce many beneficial effects to treat PCOS symptoms. There is evidence that using soy products as supplements to treat individuals with type 2 diabetes decreases fasting glucose, fasting and postprandial insulin, insulin resistance, triglycerides, low-density lipoprotein, and hemoglobin A1c.[68–70] In addition studies have indicated that increased soy intake decreases risks of endometrial cancer, hypertension, and hyperlipidemia.[71,72]

D-Chiro-inositol

Women with PCOS are believed to have a deficiency of a D-chiro-inositol-containing-inositolphosphoglycan (DCI-IPG), causing insulin resistance and hyperinsulinemia. Research has shown that D-chiro-inositol supplementation in women with PCOS increases insulin action; improves ovulation rates; and decreases androgen levels, blood pressure, and hypertriglyceridemia.[73,74]

A study done with obese women who had PCOS showed that treatment with metformin improved insulin action by increasing the insulin-mediated release of DCI-IPG mediators.[75] DCI-IPG functions to stimulate the limiting-enzymes pyruvate dehydrogenase phosphatase (involved in insulin-induced lipogenesis) and glycogen synthase phosphatase (involved in insulin-induced glycogenesis).[76]

Lifestyle Changes

Dietary changes and weight loss have been shown to have profound effects on the symptoms of PCOS. Research has indicated that even modest weight loss improves insulin sensitivity, men-

strual-cycle regularity, and fertility; increases SHBG; and decreases circulating androgens.[77] In addition, weight loss has been shown to decrease ovarian volume, number of follicles, and spontaneous abortion rates.[78]

Dietary changes can affect blood-sugar control and weight loss. Diets focused on low–glycemic-index carbohydrates, low saturated fats, and high fiber have benefited women with PCOS.[79]

Fasting and postprandial insulin levels were improved in women with PCOS on a moderately low carbohydrate diet.[80] Another study with women with PCOS showed that a low-carbohydrate ketogenic diet for 6 months led to a decrease in fasting insulin levels, percent of free testosterone, LH/FSH ratio, and weight.[81] Diets high in fiber have been shown to decrease insulin resistance in overweight or obese women as well as in healthy adults.[82,83]

Conclusions

PCOS is a complex condition for which the symptoms are variable and the cause is unknown. This makes both diagnosis and treatment of this condition challenging. Although additional research on nutrient and herbal interventions is necessary, studies have provided evidence that such supplements are effective for treating PCOS. □

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