# Polycystic Ovary Syndrome: Clinical Considerations

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Abstract
Polycystic ovary syndrome (PCOS) is one of the most frequently encountered endocrine disorders occurring in women of reproductive age. Clinically, a patient usually presents with menstrual irregularities, infertility, and hirsutism. If not treated properly, a patient is at risk for type 2 diabetes, cardiovascular disease, and hyperestrogen-related cancers. The hallmark endocrine disorders of this syndrome are hyperandrogenism and hyperinsulinemia. Great controversy exists as to which state precedes the other. There also appears to be a defect in the hypothalamic-pituitary-adrenal (HPA) axis in patients presenting with polycystic ovary syndrome. Research consistently demonstrates that the first line of treatment for this condition is weight loss. Weight loss and dietary changes appear to affect all parameters of hormonal fluctuation. Due to the vast array of side effects associated with many pharmaceutical agents typically prescribed to treat PCOS, natural therapeutics including nutrient supplementation and botanicals may be a less invasive and equally effective approach. Due to the seriousness of this syndrome when left untreated, prompt evaluation and treatment is essential.
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## Introduction

Polycystic ovary syndrome (PCOS) is a prevalent and frequently encountered endocrine disorder.[1] It has been suggested that this condition occurs in as many as 4-10 percent of women of reproductive age,[2] with onset manifesting as early as puberty.[3] Because of the diversity of clinical and metabolic findings in PCOS, there has been great debate as to whether it represents a single disorder or multiple associated pathologic conditions. PCOS is primarily characterized by hyperandrogenism, insulin resistance, and chronic anovulation.[4] Hyperandrogenism and insulin were linked as early as 1921, when Achard and Thiers published a classic description of bearded women with diabetes.[5] However, polycystic ovary syndrome was not described until 1935, when Stein and Leventhal described the syndrome as having pathognomonic ovarian findings and the clinical triad of hirsutism, amenorrhea, and obesity.[6] Today, a patient usually presents clinically with concerns regarding menstrual irregularities, infertility, and hirsutism. The syndrome is also associated with dyslipidemia and acanthosis nigricans,[7] and may increase the risk for cardiovascular disease[8] and hyperestrogen-related cancers such as endometrial[9] and breast[10] cancers. During the reproductive years, PCOS is associated with significant reproductive morbidity, including infertility, abnormal uterine bleeding, miscarriage, and other complications of pregnancy.[11]

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PCOS usually begins in adolescence, and it is difficult to predict whether the symptoms of the syndrome will self correct or persist into adulthood. Up to 50 percent of women affected with PCOS are obese, a condition that has been found to increase the magnitude of underlying insulin resistance.[12] Obesity tends to be less of a problem in women with PCOS in the adolescent population.[13] However, both the adolescent and middle age groups tend to have android body types, with waist-to-hip ratios greater than 0.8, even in the presence of normal body mass index.[12] Obesity has also been linked to increased androgen production and hirsutism.[14] Because of the wide range of symptoms and maladies associated with PCOS, thorough evaluation and diagnosis is essential to prevent further pathology.

## Pathophysiology

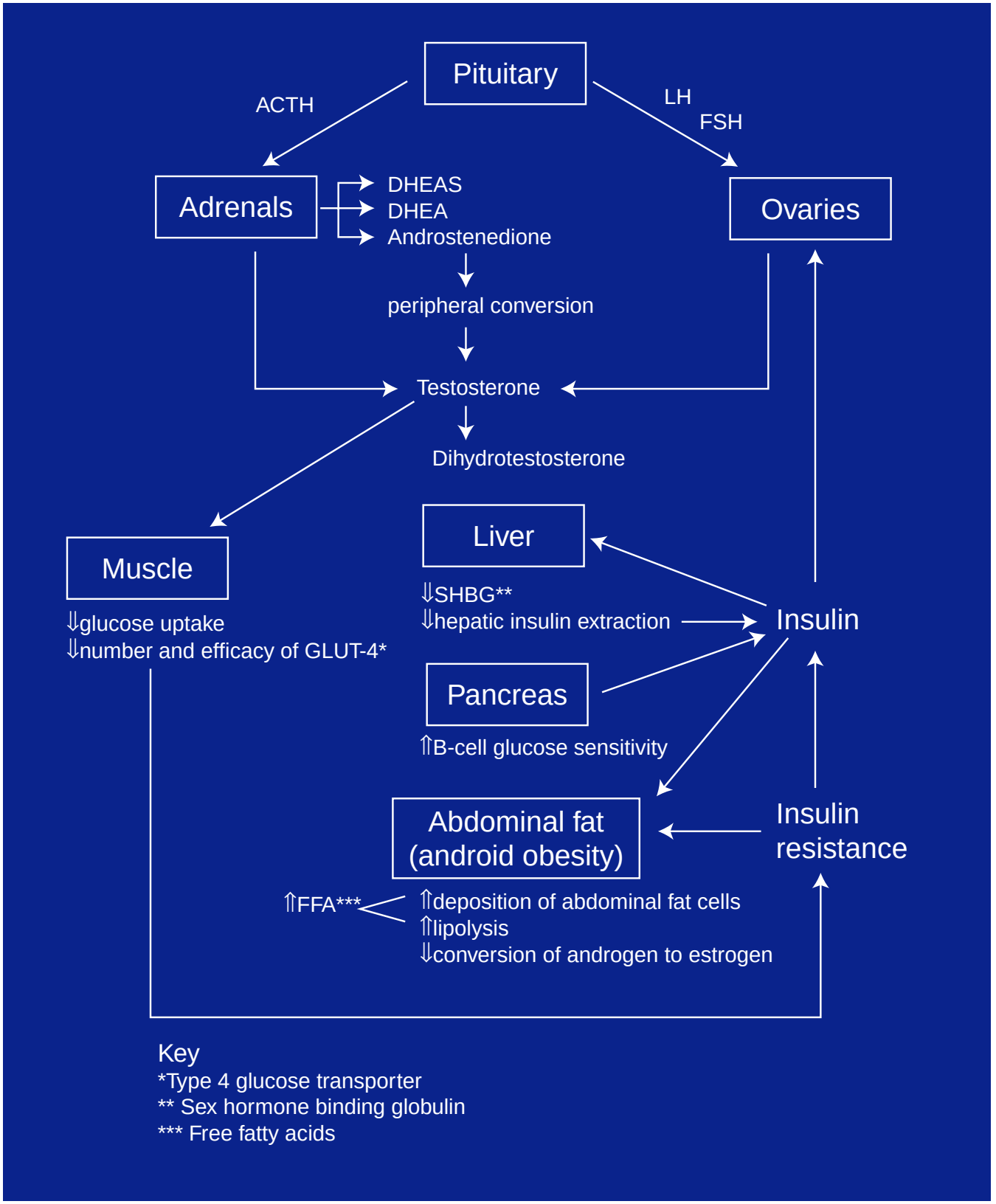
The underlying defect in polycystic ovaries remains unknown; however, there is growing consensus that the key features are androgen excess, insulin resistance, and abnormal gonadotropin dynamics. The largest question is whether the hyperinsulinemic state stimulates excess ovarian androgen production, or whether a chronic hyperandrogenic state promotes insulin resistance. There is also growing evidence of a link between chronic stress situations and multiple hormonal imbalances.

PCOS has clearly proven itself to be a disorder of excess physiological response to androgens. Once androgens reach target cells they must interact with the androgen receptor, which is encoded by a gene on the X chromosome. Testosterone is the most important circulating androgen. Approximately one-half of a woman's serum testosterone is derived from peripheral conversion of secreted androstenedione, while the other half is derived from direct glandular secretion. The ovaries and the adrenal glands contribute equally to testosterone production in women;[15] however, in PCOS the main source of androgens is thought to come from the ovaries. Dysregulation of cytochrome p450c17, the androgen-forming enzyme in both the adrenals and the ovaries, may be the central pathogenic mechanism underlying hyperandrogenism in PCOS. In the presence of 5-alpha-reductase, testosterone is converted within the cell to the more potent androgen dihydrotestosterone. Excess 5-alpha-reductase activity in the skin determines the presence or absence of hirsutism.[16] Additionally, estrone (E1) levels are increased as a result of peripheral conversion of androstenedione. Estradiol (E2) levels are normal in PCOS because they predominately occur during the follicular phase, which is not abnormal in this condition.[17] This results in a chronic hyperestrogenic state with the reversal of the E1:E2 ratio, predisposing patients to a number of further health complications.

Normally less than three percent of testosterone circulates freely in the serum. Most circulating androgens are bound, primarily to sex hormone-binding globulin (SHBG). When bound to SHBG, the hormone is considered biologically inactive. Any condition that decreases the levels of SHBG or other binding proteins can lead to a relative excess of circulating androgens. In patients with hirsutism, the major conditions that are linked with decreased SHBG levels are PCOS and obesity, independently.[18]

Androgens may both directly and indirectly result in alterations in glucose metabolism, ultimately causing a hyperinsulinemic state (Figure 1). Androgens may directly inhibit peripheral and hepatic insulin action. A study by Ciaraldi et al found that insulin receptor binding and kinase activity were intact in adipocytes of women with PCOS, although they exhibited marked decrease in insulin sensitivity for glucose transport stimulation.[19] The study concluded there was a post-binding defect present, which was probably related to the increasing androgen levels in PCOS women. This group suggested that testosterone could induce insulin resistance in these women by

**Figure 1.** The Relationship Between Androgens and Glucose Metabolism



reducing the number and efficacy of glucose transport proteins, specifically the type-4 glucose transporter (GLUT-4). GLUT-4 appears to be responsible for the insulin-related uptake of glucose in muscle and fat.

It has also been shown that women with central obesity, the type most commonly seen with PCOS, have higher free androgen levels and exhibit significantly higher levels of insulin insensitivity compared to weight-matched controls.[20] Androgens and increased free fatty acids (FFAs), common in central obesity, inhibit hepatic insulin excretion, resulting in hyperinsulinemia and insulin resistance.[21] Testosterone is known to facilitate lipolysis, providing increased FFA concentrations.[22] Even more important to this mechanism is the fact that elevated FFA levels have been shown to inhibit insulin-stimulated glucose uptake in skeletal muscle, a condition that defines insulin resistance.[23] A study by Nagamani et al examined women with ovarian hyperandrogenism and hyperinsulinemia. Following bilateral oophorectomy, hyperandrogenism was eliminated without improvement in insulin resistance.[24] This could in part be due to other related factors such as diet and family history.

Insulin resistance and compensatory hyperinsulinemia are characteristic metabolic disturbances of many, but not all, women with PCOS. Hyperinsulinemia may be central to the pathogenesis of the syndrome for some women, since it can induce hyperandrogenism and anovulation.[25] Studies have demonstrated, both *in vivo* and *in vitro,* that hyperinsulinemia stimulates ovarian androgen production and decreases the synthesis of SHBG by the liver.[26] Hyperinsulinemia in women with PCOS has proven to be associated with a higher frequency of menstrual abnormalities than in normoinsulinemic women with PCOS.[27] It has also been shown that chronic hyperandrogenism and hyperinsulinemia affect the secretion of gonadotropins in favor of increased luteinizing hormone (LH), which contributes to the mechanism of anovulation.[28]

Insulin resistance in at least 50 percent of women with PCOS appears to be related to excessive serine phosphorylation of the insulin receptor. A factor that is extrinsic to the insulin receptor, which is thought to be a serine/threonine kinase, appears to cause the abnormality. Serine phosphorylation modulates the activity of the key regulatory enzyme of androgen biosynthesis, p450c17. Therefore, it is possible a single defect produces both insulin resistance and hyperandrogenism in some PCOS women.[29]

Reports conflict regarding the presence of hypothalamic-pituitary-adrenal (HPA) axis abnormalities in women with PCOS. Anovulation is associated with disturbances in the feedback from the ovarian steroid hormones to the hypothalamus and pituitary, resulting in disturbances in the pulsatility of gonadotropin releasing hormone (GnRH) release. Gonadotropin-secretory changes, with a characteristic increase in LH relative to follicle-stimulating hormone (FSH) release, have long been recognized in PCOS.[30] It has also been suggested that the elevated concentrations of LH are due to an abnormal feedback by estrogen[31] and that the high concentrations of LH in PCOS are detrimental to follicular growth.[30]

One hypothesis suggests PCOS is caused by insufficient central β-endorphin inhibition of GnRH, thus maintaining elevated β-endorphin levels. This hypothesis is supported by studies showing β-endorphin exerts tonic inhibitory control on the GnRH pulse generator and on pituitary LH release.[32,33] The involvement of β-endorphins in PCOS is also supported by the finding that elevated β-endorphin levels in plasma are related to hyperinsulinemia. Interestingly, β-endorphin levels are also elevated following stress.[11] A second hypothesis was explored in rat studies in which experimentally-induced PCOS yielded increased levels of norepinephrine and decreased numbers of β-adrenoreceptors in the ovaries.[34] Together this would imply that PCOS

is associated with elevated sympathetic tone in the ovaries, resulting in steroidal hyperresponsiveness.

A study performed by Waldstreicher et al measured frequent (every 10 minutes) and prolonged (12-24 hours) serial blood samples which revealed a significant increase in the frequency and amplitude of LH release with normal FSH release in PCOS.[35] The increased LH pulse frequency reflects an increase in GnRH release and suggests the presence of a hypothalamic defect.[36] Ovulatory women with the polycystic morphology can have increased LH/FSH ratios; however, a single blood sample can fail to detect an increased ratio. Because of a lack of specificity, it is recommended that this ratio not be used as a diagnostic criteria.[29]

It has been demonstrated that women with PCOS have significantly higher adrenocorticotropic hormone (ACTH) and cortisol response to the administration of corticotropin-releasing hormone (CRH).[37] This suggests hyperfunction of the HPA axis as demonstrated by patients' response to Naloxone administration.[38] It is suggested that increased activity at this level could be central in origin, possibly secondary to altered sensitivity to the opioid system at the pituitary level and/or to increased opioid tone. Neuroendocrine alterations may also lead to increased sensitivity of ACTH-secreting cells to CRH.[39] It has also been demonstrated that only obese women with PCOS show HPA-axis hyperactivity in response to opioid blockade, in contrast to lean women with PCOS and lean and obese control subjects.[40]

Adrenal insufficiency may be more common in the pathogenesis of PCOS than was previously thought. It is believed that women with PCOS have a tendency toward high cortisol levels; however, when placed in a chronic stress situation, adrenal reserves are depleted. When an individual is in a state of low adrenal reserve, in the absence of significant stress, the adrenal glands are still able to produce sufficient hormones to maintain a somewhat normal state of health. However, when presented with an acute or chronic stress, there is an increased demand for adrenocortical hormones. Symptoms can range from fatigue to complete collapse, and resulting disease conditions may include menstrual irregularities, type 2 diabetes mellitus, hypertension, and autoimmune diseases.[41] With this in mind, we can speculate that individuals with chronic stress may be predisposed to conditions such as PCOS. Psychological stress appears to be more prevalent in women with PCOS.[42,43]

A study of women with PCOS evaluated adrenal androgen secretion using the ACTH stimulation test following bilateral ovarian wedge resection to surgically induce ovulation. Adrenal androgen secretions were evaluated before and again six months after surgery. The PCOS group was compared to a group of women with regular ovulatory cycles, and matched for age and body mass index. Previous to the surgery, the PCOS group showed higher basal levels of testosterone, androstenedione, 17-hydroxyprogesterone (17-OHP), and LH, with decreased SHBG. Following wedge resection, PCOS subjects exhibited significant reduction in their mean levels of testosterone, androstenedione, 17-OHP, LH, as well as an increase in SHBG. No differences were found for baseline levels of DHEA in any of the subjects.[44] The increased response of androstenedione to ACTH stimulation seems to indicate the hyperandrogen response is adrenal in origin and should be further evaluated with regard to possible stress-related conditions. It also seems likely that adrenal hyperandrogenism is maintaining the ovulatory dysfunction in some patients with PCOS. In patients with PCOS and excessive adrenal androgen secretion, treatment with glucocorticoids established menstrual regularity in only 30-66 percent of patients.[45] Previous investigators have found DHEA levels to be elevated in 70-75 percent of patients with PCOS.[46]

A study of adolescent women with PCOS found ovarian volume and ovaries with a polycystic appearance had a positive correlation with DHEA, androstenedione, and testosterone levels, supporting the view that hormone dysregulation may be an important factor.[47] Adolescents with PCOS typically present with oligomenorrhea and marked hyperandrogenism without hyperinsulinemia. This supports the notion that hyperandrogenism precedes hyperinsulinemia.

## Diagnostic Criteria

PCOS is known to be associated with reproductive morbidity and increased risk for endometrial and breast cancer; therefore, early diagnosis is extremely important. PCOS is thought to be linked to metabolic and cardiovascular risks, making preventive therapy crucial. A thorough history must be taken, including the timing and chronological expression of symptoms. The onset of pubertal development and menstrual regularity is important, as any evidence of precocious puberty is often associated with androgen hyperactivity.[16] Menstrual irregularities range from symptoms of amenorrhea (cessation of menses), to oligomenorrhea (infrequent menses), to menorrhagia (excessive duration or amount of bleeding).[48,49] Family history is important in establishing links between onset of puberty, menstrual irregularities, diabetes, and familial patterns of hair growth. Studies show that PCOS has a genetic component, most likely with an autosomal dominant mode of transmission.[50]

Physical examination should focus on establishing the presence and extent of hirsute symptoms, such as acne and excessive hair growth. Hip-to-waist ratios and body mass index are also important parameters to measure. On gynecologic exam, palpation of the ovaries should be performed to assess for cysts. Additionally, a cardiovascular evaluation should be made if the patient is in her third decade or beyond or has high blood pressure.

In 1990, the National Institutes of Health formed a group to investigate PCOS. Even though no consensus was reached regarding the name of this disorder, which remains controversial to date, diagnostic criteria were determined.[51] The consensus was that women who present with hyperandrogenism and chronic anovulation, in the absence of congenital adrenal disorders, Cushing's syndrome, hyperprolactinemia, or tumors should be diagnosed with PCOS.[52]

Excess androgen production is the most common trigger for hirsutism, which appears on physical exam as excessive, coarse hair in an abnormal pattern.[53] This definition highlights the abnormal distribution of excess hair growth, such as facial, chest, or upper abdominal hair. Virilization refers to the concurrent presentation of hirsutism with a broad range of signs suggestive of androgen excess, such as acne, fronto-temporal balding, deepening of the voice, a decrease in breast size, clitoral hypertrophy, increased muscle mass, and amenorrhea or oligomenorrhea. Hirsutism and virilization are closely linked; however, hirsutism often precedes virilization if left untreated. Although the source of androgens can be exogenous, it is most commonly endogenous as a result of adrenal and ovarian production.[16] Hirsutism may develop peripubertally or during adolescence, or it may be absent until the third decade of life.[52] Some women with PCOS never develop signs of androgen excess because of genetic differences in receptor number or tissue sensitivity.[42]

Initial laboratory testing for the assessment of hirsutism should include total and/or free testosterone, dehydroepiandrosterone sulfate (DHEAS), and 17-hydroxyprogesterone measurements. Normal values for serum androgens are listed in Table 1. If a patient is also oligomenorrheic, LH, FSH, prolactin, and thyroid-stimulating hormone tests may be useful as well. Serum testosterone level is the best marker for ovarian hyperandrogenism, and DHEAS is the best

**Table 1.** Relative Risks of Cardiovascular Events According to Baseline Plasma Levels of Markers of Inflammation and Lipids

| Serum Androgens | Value |
|---|---|
| Testosterone | 20-80 ng/dL |
| Free Testosterone | 0.3-1.9 ng/dL |
| Androstenedione | 20-250 ng/dL |
| Dehydroepiandrosterone sulphate | 100-350 ng/dL |
| 17-Hydroxyprogesterone (follicular phase) | 30-200 ng/dL |

adrenal marker. It is recommended that these levels be measured. Free testosterone provides a better diagnostic yield for ovarian hyperandrogenism because levels of SHBG are decreased thus increasing free hormone levels. Clinical assays used to test this measure vary considerably, perhaps affecting reliability.

When any anovulatory state exists for any period of time, the "polycystic ovary" emerges. Approximately 75 percent of anovulatory women from any cause have polycystic ovaries.[49] The ovarian diagnosis is confirmed by ultrasound, with findings of bilaterally enlarged polycystic ovaries. The ovary is usually greater than 9mL with more than 8mL peripherally oriented cystic structures in a sonographic plane by an increased stromal mass (>25% of the ovarian volume).[48] Classification of polycystic suggests there are eight or more follicles present, with the follicles less than 10 mm in diameter.[54] These ultrasound findings appear to be present in more than 90 percent of women with PCOS; however, they are also present in up to 25 percent of "normal" women.[55] Ultrasonography alone is not sufficient to diagnosis PCOS.

A spectrum of sonographic results may be found. Polycystic ovaries may sometimes be absent in women with all other classic clinical characteristics of PCOS. This may be in part due to the resolution of ultrasonographic technique. For example, abdominal ultrasounds are much less sensitive than trans-vaginal scans.[1] Since ultrasound diagnosis alone is not sufficient to diagnose PCOS, similar treatment protocols should be considered in cases where endocrinologic findings exist, but no polycystic ovaries are found. At the same time, the presence of polycystic ovaries alone is not consistently linked to clinical or biochemical abnormalities as evidenced by a study of postmenarchal women (ages 18-25 years) recruited from the general population for a women's health study.[56] This study detected the presence of polycystic ovaries in 33 percent of the population, suggesting this may be a "normal variant" of ovarian morphology. These findings can only be confirmed by performing a large-scale prospective study to follow this group of women to determine any long-term risks. Table 2 outlines some of the most important diagnostic criteria for PCOS.

**Table 2.** Diagnostic Criteria for PCOS

| |
|---|
| **Clinical Features:** |
| Abnormal menses: amenorrhea, oligomenorrhea, menorrhagia<br>Anovulatory infertility<br>Hirsutism and/or acne<br>Central obesity |
| **Endocrine abnormalities on Laboratory Tests:** |
| Elevated androgen levels (testosterone)<br>Elevated LH concentration<br>Normal to mildly elevated FSH level<br>Insulin resistance with hyperinsulinemia |
| **Ultrasound examination:** |
| Multiple subcortical follicular cysts<br>Increased ovarian stromal density and/or volume |
| **Differential Diagnosis:** |
| Congenital adrenal hyperplasia<br>Cushing's syndrome<br>Adrenal or ovarian tumor<br>Prolactinoma |

## Conventional Treatment

Many of the treatments being used to treat PCOS are pharmaceutical agents that were designed to treat conditions such as hyperinsulinemia, hirsutism, and benign prostatic hyperplasia (BPH). Antiandrogens, alone or in combination with oral contraceptives, are considered to be the conventional treatment of choice.[57] Combination estrogen-progesterone oral contraceptives suppress gonadotropin secretion, reducing ovarian androgen synthesis while simultaneously establishing a normal menstrual cycle.[58] Many antiandrogen treatments reduce hirsutism and circulating levels of androgens, triglycerides, and low density lipoprotein (LDL), but they fail to restore menstrual cyclicity, reduce hyperinsulinemia, or increase high density lipoprotein (HDL).[59,60] Because hyperinsulinemia often plays a role in the pathogenesis, insulin-sensitizing agents have been tried as a sole treatment of metabolic as well as reproductive dysfunction.

Metformin, an insulin-sensitizing agent commonly used to treat type 2 diabetes, has been reported to reduce ovarian cytochrome p450c17 activity, improve hyperandrogenism, and restore ovulation in women with PCOS.[61] In a study by Ibanez et al, adolescent girls with clinically and biochemically defined PCOS showed significant improvement in symptoms associated with hirsutism, free androgen index, circulating total testosterone, androstenedione, and DHEAS. Regular cycles were reported by all girls within four months of beginning treatment.[62] The primary mechanisms of action of metformin are to increase glucose uptake by fat and muscle and to improve insulin-stimulated glucose disposal.[63] Studies by Velazquez et al found metformin improved insulin sensitivity and decreased androgens while normalizing the LH/FSH ratios in women with PCOS.[64] Side effects of metformin include lactic acidosis and malabsorption, including poor absorption of vitamin B12.[65]

Antiandrogen therapy includes pharmaceutical agents that inhibit androgen synthesis (ketoconazole), block 5-alpha-reductase (finasteride), or interact with androgen receptors preventing the biological actions of androgens on their target tissue (cyproterone acetate, spironolactone, flutamide).

Ketoconazole is an imidazole derivative used for the treatment of fungal disease. It blocks adrenal and gonadal steroid synthesis by inhibiting p450scc, p450c17, 3-beta-hydroxysteroid dehydrogenase, and p450c11 enzymes. Treatment may have beneficial effects on hirsutism, but long-term treatment suppresses cortisol synthesis and can cause severe liver toxicity.[66]

Finasteride is a 5-alpha-reductase inhibitor used in the treatment of BPH. It inhibits androgen action by decreasing the production of 5-alpha-dihydrotestosterone, the most potent ligand for the androgen receptor.[65] Finasteride appears to have no effects on the circulating levels of testosterone and gonadotropins. Although no side effects have been noted in women treated with finasteride, it has been shown in rat studies to cause ambiguous genitalia in male offspring of female rats.[67] Therefore, it is suggested to avoid taking this pharmaceutical during pregnancy.

Cyproterone acetate (CPA) is a known steroidal antiandrogen derived from 17-hydroxyprogesterone. It is a potent progestin that possesses antiandrogenic and glucocorticoid activity. It is one of the most well-established therapeutics for the treatment of hirsutism and has also shown promise for the treatment of acne.[68] CPA blocks androgens by competitively binding to the androgen receptor. In cases of PCOS it is usually given in conjunction with estrogen, primarily in the form of a contraceptive, in order to prevent possible bleeding complications. Side effects of CPA include weight gain, fluid retention, mood changes, headaches, breast tenderness, and decreased libido. Many of the side effects may be due in part to the glucocorticoid activity of the drug.[68]

Spironolactone (SP) is an antihypertensive diuretic agent used either alone or in combination with other therapies. SP acts as an androgen-receptor antagonist at the hair follicle and also decreases androgen synthesis by inhibiting the microsomal cytochrome p450 system.[70] SP also appears to have a direct inhibitory effect on 5-alpha-reductase, specifically in the skin. Side effects of this treatment may include mild diuresis, weakness, fatigue, weight gain, breast enlargement and tenderness, and dizziness.[71] The most common side effect of this treatment is irregular uterine bleeding. Therefore, SP is given in combination with oral contraceptives.[72]

Flutamide is most commonly used for prostate cancer. It is a nonsteroidal antiandrogen that has also been found to be effective in the treatment of the skin manifestations of hyperandrogenism – acne and hirsutism.[73] Flutamide itself is a weak antiandrogen; but upon digestion it is converted to a more potent antiandrogen, 2-hydroxyflutamide. Together, flutamide and 2-hydroxyflutamide inhibit the binding of 5-alpha-dihydrotestosterone to the androgen receptor, inhibiting testosterone biosynthesis.[74] The most common side effect of flutamide is dry skin, although symptoms such as increased appetite and weight gain have been reported. More importantly, flutamide has the potential to cause fatal drug-induced liver failure in less than 0.5 percent of patients on this medication.[75]

## Lifestyle Interventions

Because of potential side effects of many medications, weight reduction of obese patients should be the primary goal of treatment. The addition of antiandrogenic and insulin regulating agents should be added only to enhance the effects of weight loss. Experimental evidence has indicated that the typical

western diet, which is high in fat and refined carbohydrate and low in fiber, induces insulin resistance and precedes obesity.[76] Epidemiological evidence indicates that a diet rich in fruits, vegetables, and high fiber complex carbohydrates is associated with a lower risk of chronic disease.[77,78] Studies of obese women with menstrual abnormalities have demonstrated that cycles can potentially normalize and fertility be re-established following weight loss.[79,80] Traditionally, sex steroids and thyroid hormones have been considered to be the major regulators of SHBG concentration, but dietary factors may be a more important consideration.

It has been shown that short-term treatment of obese PCOS women on a very low calorie diet (350-450 kcal per day) leads to a two-fold increase in serum SHBG levels and an accompanying fall in serum insulin.[81] This prompted a second study by the same group to question whether long-term calorie restriction and weight reduction could not only improve hormone levels, but also restore regular ovulatory menstrual cycles and fertility. Results showed that with weight loss of less than five percent there was not only significant biochemical improvement but clinical as well. Reversal of ovarian dysfunction was striking, with 82 percent of women in the group showing marked improvement in fertility, including five pregnancies in women who had long standing infertility.[82]

Insulin sensitivity has also proven to be influenced by dietary modifications, especially a low glycemic diet. Because circulating FFAs have an influence on insulin sensitivity in muscle and adipose tissue, the sensitivity of adipose tissue to insulin is thought to be a determinant of general insulin sensitivity.[83] Metabolic changes occur with increasing visceral obesity, including fasting hyperinsulinemia and decreased plasma HDL cholesterol. These metabolic atherogenic changes associated with abdominal obesity are thought to result from increased FFAs reaching the liver as a consequence of reduced visceral adipocyte insulin sensitivity.[84] This net effect suggests the body needs to decrease glucose oxidation and hepatic insulin clearance while increasing hepatic glucose production. This can be achieved by eating a low glycemic diet. The glycemic index of a carbohydrate is a measure of its postprandial effect on blood glucose.[85] The lower the glycemic index, the smaller the effect of the carbohydrate on postprandial glucose and insulin values. Because of the correlation between PCOS and hyperinsulinemia, a low glycemic diet could potentially decrease hyperinsulinemia with greater regulation of FFAs postprandially.

Recently Longcope et al analyzed data from a large cross-sectional sample from the Massachusetts Male Aging Study. After controlling for a number of confounding variables, the authors concluded that fiber intake was found to be significantly positively correlated to serum SHBG concentrations, whereas protein intake showed a clear negative association with SHBG.[86] The authors propose that as protein ingestion is known to inhibit insulin secretion, insulin has in turn been shown to inhibit hepatic SHBG production. However, dietary carbohydrate intake, a stimulus for insulin release, did not show significant association with SHBG. It is further thought that the relationship of protein to SHBG levels involves more than only an effect on insulin. Further studies need to be performed to evaluate this role.

Studies have been designed to explore caloric content and the role of dietary fat in the regulation of energy intake and weight loss. A study was performed to evaluate caloric consumption in women who each consumed a sequence of three two-week diets of low, medium, and high fat content. Results showed that by altering the type of food consumed, specifically fat, even without restrictions on amounts, spontaneous weight loss could be achieved in both obese and non-obese individuals on a low fat diet.[87]

Eating disorders and body image problems often begin in adolescence and are carried into adulthood. Because women with PCOS are often instructed by their physician to lose weight, it is important to encourage safe dietary practices. PCOS has been associated with a high incidence of eating disorders, including binge eating and fasting.[88] The extreme variations in energy intake of these behaviors may contribute to or exacerbate insulin resistance as well as be associated with thyroid conditions, particularly hypothyroidism. All women with PCOS should be evaluated for eating disorders, especially in the adolescent population.

Physical exercise can be an important adjunct in the prevention and treatment of insulin resistance. In the context of overall glucose homeostasis, a single instance of exercise can markedly increase rates of whole body glucose disposal[89] and increase the sensitivity of skeletal muscle glucose uptake to insulin.[90] These effects can last for several hours after completion of exercise. During insulin-stimulated conditions, fatty acid oxidation in skeletal muscles is normally suppressed, yet incomplete suppression of fatty acid oxidation occurs in obesity-related insulin resistance.[91] A prospective clinical study revealed that reduced fatty acid oxidation is a metabolic risk factor for weight gain and that enzyme activities within skeletal muscle pertaining to lipid metabolism might contribute to lower fatty acid concentrations.[92,93] Moreover, after weight loss, skeletal muscle in post-obese individuals may continue to be inefficient in the oxidation of fat. Reduced activity of oxidative enzymes in skeletal muscle has been found in obesity and insulin resistance.[94] Improvements in insulin responsiveness can last up to two weeks in trained individuals, but can begin to decline within one week in untrained or obese individuals. This clearly indicates that regular physical activity is required to have a lasting effect on insulin responsiveness.

In an observational study of adolescent women with PCOS, van Hooff et al found a significant decrease in the frequency of self-reported acne, dysmenorrhea, and menstrual irregularities in those engaging in more than eight hours of sporting activity per week.[47] Although few studies have reported on the link between exercise and PCOS, clear associations have been made with regard to exercise and its effects on obesity and insulin resistance.

## Nutritional Supplementation

Many of the conventional treatments being utilized are not specific for PCOS but have been used because the mechanisms of action indicate a potential benefit. There are a number of natural products which may have potential benefit without the possible side effects of abnormal uterine bleeding, weight gain, and liver failure seen with some of the conventional approaches.

### Dietary Fiber

The health benefits of dietary fiber in reducing the risk of chronic disease have been well-established.[95] Several characteristics of dietary fiber have been established, including the bulking effect that increases fecal volume, limits caloric intake, slows stomach emptying, and dilutes the content of urine.[96] Dietary fiber also has the capacity to bind and eliminate organic compounds, which could reduce the interaction of potentially carcinogenic compounds within the intestinal mucosa. Several lines of evidence also suggest that dietary fiber may play a key role in the regulation of circulating insulin levels. Fiber reduces insulin secretion by slowing the rate of nutrient absorption following a meal.[97] Studies show that insulin sensitivity increases[98] and body weight decreases in people on high fiber diets.[99] A recent study in *The Journal of the American Medical Association (JAMA)* confirmed that fiber consumption could predict insulin levels, weight gain, and other

cardiovascular risk factors more strongly than saturated fat consumption. [100]

## Flaxseed

Flaxseed is one of the most significant sources of plant lignans, one of the main classes of estrogenic compounds called phytoestrogens.[101] Phytoestrogens represent a family of plant compounds that have been shown to have both estrogenic and antiestrogenic properties. Flaxseed and its isolated lignans have been shown to have numerous chemoprotective effects both *in vitro* and *in vivo*. Many of the chemoprotective effects may be mediated through their influence on endogenous sex hormone production, metabolism, and biological activity. Consumption of flaxseed and its isolated lignans have been shown to stimulate SHBG synthesis,[102] as well as reduce mammary tumor growth[103] and formation.[104] Changes in total hormone concentration result in relatively small changes in the size of free hormone fraction, whereas changes in SHBG concentration result in relatively large changes in the amount of free and bound hormones. Both lignans and isoflavones have been reported to stimulate the synthesis of SHBG by Hep G2 liver cancer cells in culture.[105] This is consistent with an observational study of 34 women in whom urinary lignan concentrations significantly and directly correlated with SHBG concentrations and inversely correlated with the proportion and concentration of free estradiol.[106] Although the association between the intake of phytoestrogens, specifically flaxseed, and increases in SHBG concentration is still quite weak, it shows great potential for phytoestrogens as a means of reducing free estrogen concentrations.[105]

## Fish Oil

Adjusting the quality of food eaten – specifically fats – appears to be an important component of treatment of PCOS. The fatty acid components of dietary lipids not only influence hormonal signaling events by modifying membrane lipid composition, but fatty acids may directly influence molecular events that govern gene expression. It is thought that this regulation of gene expression by dietary fats has the greatest impact on the development of obesity and insulin resistance.[107] Fish oils, which are comprised of the essential fatty acids eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3), fall into a larger category of fats called polyunsaturated fatty acids (PUFAs). Compared to other types of fats, PUFAs are more readily used for energy and enhance the rate of glycogen storage, which allows the skeletal muscle to increase its uptake of glucose, even under conditions where fatty acid oxidation is accelerated. The same studies have also found that ingestion of fish oils decreases lipid droplet size and number, which has been found to improve insulin sensitivity.[108] More specifically, fish oils have been shown to increase thermogenesis, decrease body fat deposition, and improve glucose clearance.[107] Clinical trials have shown that a dose of 4 g/day is effective at regulating postprandial lipemia.[109]

## D-chiro-inositol

Recent studies have suggested that women with PCOS may have insulin resistance and hyperinsulinemia due to a D-chiro-inositol deficiency. D-chiro-inositol is a component of a phosphoglycan that has been shown to mediate the action of insulin. The amount of chiro-inositol in muscle has been shown to be lower in subjects with type 2 diabetes than in normal subjects.[110] A study in *The New England Journal of Medicine* by Nestler et al found that 1200 mg D-chiro-inositol daily had multiple beneficial effects in the treatment

of PCOS.[111] Not only did inositol increase the action of insulin, but 86 percent of the women ovulated during treatment with D-chiro-inositol compared to only 27 percent in the placebo group. Serum androgen levels also decreased in the treatment group, as did ovarian androgen production as reflected by a decreased 17α-hydroxyprogesterone response to leuprolide. Additionally, the women in the treatment group had decreases in both systolic and diastolic blood pressures and plasma triglyceride concentrations.

## Chromium

Chromium is one of the most widely studied nutritional interventions in the treatment of glucose- and insulin-related irregularities. While research shows a clear link between chromium and glucose metabolism, evidence for its interaction in insulin resistant states is a bit more ambiguous. Chromium picolinate is the form of chromium which has been used in a number of studies on insulin resistance. In a study by Anderson et al on non-diabetic individuals with moderate post-glucose challenge hyperglycemia, a dose of 200 mcg chromium picolinate resulted in improvements in both glucose tolerance and circulating insulin levels. These changes were assumed to be due in part to increased tissue sensitivity to insulin.[112] Further studies by Anderson et al investigated the use of chromium picolinate as the sole treatment for type 2 diabetic patients. Patients were instructed to resume normal dietary and lifestyle habits during the treatment period. Subjects were assigned to one of three treatment groups: placebo, 100 mcg chromium picolinate twice daily, or 500 mcg chromium picolinate twice daily. Both fasting and two-hour postprandial glucose levels significantly decreased for both chromium treatment groups, suggesting an improvement in insulin resistance with chromium supplementation.[113]

## Botanical Influences

### *Urtica Dioica*

*Urtica dioica*, more commonly known as stinging nettle, has proven to have *in vitro* effects on SHBG. The roots of the stinging nettle contain a complex mixture of water and alcohol-soluble compounds including lectins, phenols, sterols, and lignans. The positive effects of the nettle extract are thought to be due to the lignans, which are predominantly in the glycoside form. The glycosides are cleaved in the digestive process with the intestinal microbial transformation products displaying a binding affinity to SHBG.[114] Furthermore, lignans may influence the blood levels of free, active steroid hormones by displacing them from the SHBG binding site.[115] Steroid hormones, as well as Urtica lignans, may inhibit the binding of SHBG to its receptor. This reaction would cause an increase in SHBG levels. SHBG is an allosteric protein in which the protein-receptor interaction depends on the occupancy of the steroid binding site. Bound to the receptor, SHBG is still able to bind to sex steroids, which results in the generation of the second messenger cAMP inside the cell.[116] This reaction depends on the lignans of SHBG. An *in vitro* study by Hryb et al, examining the binding of SHBG to a soluble extract of human prostatic membranes, showed a dose-related inhibition of binding of SHBG to its receptor, thus increasing the levels of circulating SHBG.[117] Although no human studies have been done, *U. dioica* root shows great promise in the treatment of PCOS by up-regulating circulating SHBG.

### *Serenoa Repens*

*Serenoa repens* (saw palmetto) is one of the most widely used botanicals in the treatment of BPH. Once again, although studies have not been conducted on the use of Serenoa in the treatment of PCOS, this herb has been found to be comparable to the pharmaceutical agent finasteride for the treatment of

BPH. The therapeutic extract is from the dried ripe fruit of the American dwarf saw palmetto plant. The Native Americans in Florida first used berries from the saw palmetto in the early 1700s to treat testicular atrophy, erectile dysfunction, and prostate gland swelling or inflammation.[118] The mechanisms of action are not completely understood, but are believed to involve altered cholesterol metabolism,[119] and antiestrogenic, antiandrogenic, and anti-inflammatory properties.[120] In an *in vitro* study by Bayne et al Serenoa exhibited marked inhibition of 5-alpha-reductase on epithelial and fibroblastic cells from samples of prostate tissue of men with BPH. Samples were obtained from the men following transurethral resection. The study also demonstrates that PSA levels did not rise with administration of Serenoa, suggesting this botanical does not interfere with other androgen-dependent processes, as do some pharmaceutical agents like the drug finasteride.[121]

A study in *JAMA* reviewed 18 randomized, controlled trials involving men with symptomatic BPH and treatment with a preparation of Serenoa alone or in combination with other phytotherapeutic agents. Sixteen of the studies were double-blinded. Treatment groups received either Serenoa, a placebo, or another pharmacological therapy for BPH. Overall, compared to men receiving placebo, men treated with Serenoa had notable improvement in self-rating of urinary tract symptoms, suggesting improvement in androgen regulation. A dosage of approximately 320 mg/day has been established as a safe and effective dose for the treatment of BPH and other androgen-related conditions.[122] Studies on its use in PCOS are warranted.

### *Vitex agnus-castus*

*Vitex agnus-castus*, commonly known as chastetree berry, has traditionally been used to treat menstrual irregularities, specifically to help establish a normal menstrual cycle and improve fertility. Vitex does not contain hormones but it is thought to exert hormonal activity by its action on the pituitary gland, specifically on the production of luteinizing hormone. It is thought Vitex has an adaptogenic effect on the anterior pituitary in the regulation of LH release. LH stimulates corpus luteal secretions after ovulation to produce progesterone, which ultimately regulates a woman's cycle. A double-blind study was conducted on 96 women with infertility, using 1.8 mL Vitex extract or placebo for three months. Results demonstrated that 56 percent of women using Vitex either became pregnant or resumed normal menstruation. The same group of women also had an increase in luteal hormone concentrations, compared to only 36 percent in the placebo group.[123] During the trial a total of 15 pregnancies occurred. The use of Vitex in the treatment of PCOS-related menstrual irregularities appears to show promise with regard to helping establish normal menstrual cycles and fertility.

## Other Treatment Options

Treatments for PCOS should not be limited to the above-mentioned therapies, but should be inclusive of therapies meant to detoxify the liver, specifically the cytochrome p450 pathways. This would help establish adequate hormone metabolism and enhance hepatic insulin clearance. Further treatment options could include optimizing adrenal function, so that the body would be better able to handle both physical and mental stress. Table 3 outlines some of the most potentially promising nutrient and botanical interventions for PCOS.

**Table 3.** Potential Beneficial Roles of Selected Nutrients and Botanicals in PCOS

| | Improves Insulin Activity | Improves Blood Glucose Control | Improves Circulating Hormone Levels |
|---|---|---|---|
| Flaxseed | | | * |
| Fish Oil | * | * | |
| D-chiro-inositol | * | | * |
| Chromium | * | * | |
| Urtica dioica | | | * |
| Serenoa repens | | | * |
| Vitex agnus-castus | | | * |
| Fiber | * | | |

## Conclusion

Sixty-five years have passed since polycystic ovary syndrome was initially described, and some 84,000 articles have been published discussing medical issues regarding this syndrome. However, there still appears to be a substantial amount of uncertainty as to what its definitive pathophysiology is. There is inherent bias when it comes to studies of PCOS that constrain the assessment of the frequency of associated clinical and biochemical findings. Studies that use an increased LH/FSH ratio as a selection criterion will be biased toward finding increased pulsed LH release when gonadotropin secretion is being examined. In studies examining clinical manifestations of hirsutism, presence of hirsute symptoms will be viewed as an essential diagnostic criterion. To date the prevalence of PCOS and associated symptomatology remain somewhat subjective. Clinical outcomes following the withdrawal of successful treatments have rarely been examined.

Because women with PCOS have an increased risk for endometrial and breast cancer due to longstanding unopposed estrogen stimulation, their menstrual function must be continually monitored well into their menopausal years. On the other hand, chronic levels of androgen excess have been shown to exert a positive influence on bone mineral density. Studies have shown that the presence of polycystic ovaries on ultrasound is associated with a higher bone mineral density compared with normal appearing ovaries, regardless of whether the endocrine system was overtly affected.[3] It is believed that exogenous androgens positively influence bone density in older women, independent of estrogen.[124] Androgenic hormones are now being used as a supplemental agent in the treatment and prevention of osteoporosis in postmenopausal women.

Because of the link between PCOS, obesity, and decreased insulin sensitivity, glucose regulation should be monitored regularly.

Studies have shown that by age 30, 25-30 percent of obese women with PCOS will have either impaired glucose tolerance or type 2 diabetes.[125] A study by Conn et al revealed that 82 percent of women with type 2 diabetes had polycystic ovaries on ultrasound. Of those women, 52 percent had clinical evidence of hyperandrogenism and/or menstrual irregularities.[126] Because of the complex nature of this disease, it is important that women with PCOS be educated about and understand the health implications related to the syndrome.

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