

Phytotherapy for Polycystic Ovarian Syndrome (PCOS)

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Polycystic ovarian syndrome (PCOS), also known as Stein-Leventhal syndrome, is a common gynecological disorder characterized by hypergonadotrophism, hirsutism, obesity, oligomenorrhea and commonly associated with infertility.¹ PCOS is a complex clinical picture and presents a multifaceted etiology related to imbalance of the hypothalamic-pituitary-adrenal (HPA) axis, thyroid involvement and metabolic syndrome (insulin resistance).¹ There is substantial evidence that PCOS should no longer be considered purely a gynecological disorder, but rather a complex endocrine disorder.²

PCOS affects approximately 5 to 10% of women of reproductive age and is one of the most common causes of anovulatory infertility.² Menstrual disruption typically manifests in PCOS, ranging from oligomenorrhea to amenorrhea.

Etiology

Despite the extensive investigations, the etiology of PCOS remains poorly understood. The most recent knowledge indicates that abnormal insulin response to glucose stimulus is a key underlying factor in PCOS.^{2,3} Other etiological factors include derangement of the sympathetic nervous control of the ovaries,⁴ estrogen dominance and elevated androgens. Some of the literature suggests a genetic susceptibility to insulin stimulation of androgen secretion, blocking follicular maturation.

Insulin Resistance

PCOS and insulin resistance are intimately related endocrine disorders. The most common causes of insulin resistance are obesity, poor diet and stress. Hyperinsulinemia is not a characteristic of hyperandrogenism in general, but is uniquely associated with PCOS.²

In obese women with PCOS, 30 to 40% of these have impaired glucose tolerance or diabetes. However women with ovulatory hyperandrogenism can present with normal insulin and glucose tolerance,^{1,2} indicating additional factors are potentially involved in the etiology.

Elevated Androgens

The ovarian and adrenal glands of women with PCOS are usually the sites of production of elevated androgens. It is postulated that these women have a hyperactive production of CYP17 enzyme, which is responsible for forming androgens in the ovaries and adrenals (from DHEA-S).² Elevated total and free testosterone correlate with the typically elevated LH levels. Serum total testosterone is usually up to twice the normal range (20 to 80 ng/dL). High androgen levels in the ovary inhibit FSH, thereby inhibiting development and maturation of the follicles.^{1,2}

DHEA is found to be elevated in 50% of women with PCOS.² The elevated DHEA is due to stimulation by ACTH, produced by the pituitary in response to stress. The excess DHEA then converts to androgens via adrenal metabolism, which in turn contributes to the typical elevated androgen levels in PCOS.

The skin and adipose tissue add to the complex etiology of PCOS. Women who develop hirsutism have the presence and activity of androgens in the skin which stimulate of abnormal patterns of hair growth. Aromatase and 17-beta-hydroxysteroid activities are increased in the fat cells and peripheral aromatization increases with body weight. The metabolism of estrogens by way of 2-hydroxylation and 17-alpha-oxidation is decreased. Estrogen levels increase as a result of peripheral aromatization of androstenedione. This cascade results in a chronic hyper-estrogen production (estrogen dominance).²

Hirsutism occurs in 70% of women with PCOS in the USA, as opposed to only 10 to 20% of Japanese women diagnosed with PCOS.³ This may be explained by the genetically determined differences in 5-alpha-reductase activity between different cultures, or from a holistic standpoint, may reflect differences in endocrine behavior in accordance with local diet and levels of physical fitness.

Estrogen Dominance

The hypothalamic-pituitary axis imbalance can contribute significantly to the etiology of PCOS. The result of increased gonadotrophin releasing hormone (GnRH) output causes

an elevation in the pulsatile output of LH and results in an elevated LH to FSH ratio (typically 2:1 respectively).^{2,5} FSH is not increased as a result of elevated LH in this case, likely due to the hypothalamus responding via negative feedback to the already chronically elevated estrogen levels.

About 25% of PCOS patients exhibit elevated prolactin,^{1,2} known as hyperprolactinemia. Hyperprolactinemia results from abnormal estrogen negative feedback via the pituitary gland. Elevated prolactin can in turn contribute to elevated estrogen levels.

PCOS Holistic Diagnostic Criteria

Menstrual irregularity

- Eight or fewer menstrual cycles per year
- Unpredictable menstrual cycles
- Amenorrhea for longer than 4 months in the absence of pregnancy or menopause
- Infertility
- History of ovarian cysts
- Irregular bleeding
- Excessive or heavy bleeding

Skin complications

- Adult acne
- Severe adolescent acne
- Cystic acne on face, neck, back shoulders
- Hirsutism with excessive hair on face, body, upper lip, chin, neck, abdomen
- Thinning of the head hair or male pattern balding
- Acanthosis nigricans: discoloration or darkening of skin (may be in patches) around neck, groin, under arms, skin folds or skin tags (see later)

Insulin resistance

- Weight gain, especially around trunk (apple body shape or android body shape, especially after the age of 30 years)
- Dysglycemia
- Difficulty losing weight
- Family history of diabetes or menstrual irregularity

Obesity is found in 50% of patient with PCOS.^{1,2,5} The body fat is usually located centrally around the trunk. A higher waist to hip ratio indicates an elevated risk of cardiovascular disease and diabetes.¹ Insulin resistance and metabolic syndrome are commonly seen in PCOS patients and insulin resistance is now recognized as a risk factor for the development of diabetes mellitus type 2.

Approximately one-third of obese PCOS patients have impaired glucose tolerance and up to 10% have diabetes mellitus type 2.² Acanthosis nigricans, a condition in which the vulva develops thickened, pigmented velvety lesions, is considered a marker of insulin resistance in women with hirsutism. These lesions can also be found on the nape of the neck, inner thigh and below the breast. Women with

severe insulin resistance can develop HAIR-AR syndrome consisting of hyperandrogenism (HA), insulin resistance (IR) and Acanthosis nigricans (AR).^{1,2} These women will have elevated testosterone (>150 ng/dL) and fasting insulin levels of greater than 25 µIU/dL. Insulin alters steroidogenesis (independent of gonadal production) in PCOS, as insulin and insulin-like growth factor receptors are located within the ovarian tissue.²

Associated with impaired glucose tolerance is the abnormal lipoprotein profile that can be seen commonly in patients with PCOS. The typical PCOS lipoprotein profile includes:

- Elevated total cholesterol
- Elevated triglycerides
- Elevated low density lipoproteins (LDL)
- Low high density lipoproteins (HDL)
- Low apoprotein A-1²

The culmination of these factors leads to a marked elevation in cardiovascular risk for the PCOS patient. Another metabolic observation that puts these women at higher cardiovascular risk is the incidence of impaired fibrinolysis, shown by elevated circulating levels of plasminogen activator inhibitor. This is associated with atherosclerosis and hypertension. When these factors are combined, PCOS women are at much higher risk of hypertension, atherosclerosis, and exhibit a seven-fold risk of myocardial infarction.²

Recommended naturopathic hormonal evaluation:

- Salivary Adrenal Stress Index, including ACTH
- Salivary or serum expanded female hormonal panel, including testosterone and LH to FSH ratio
- Glucose tolerance test
- Thyroid panel
- Blood lipid profile

Typical hormonal disturbances associated with PCOS diagnosis include:

- LH is elevated while FSH is usually low at a ratio of 2:1
- Progesterone can be low
- Sex Hormone Binding Globulin (SHBG) is usually low
- Androgens such as testosterone and DHEA-S are usually elevated

Conventional Treatment Approaches

The conventional treatment for PCOS is dependent on the patient's desired goal of either menstrual regularity in order to achieve pregnancy or menstrual regularity for contraception. Some women seek treatment for the removal of excessive male hair growth patterns, such as increased facial hair (common to women with PCOS and elevated androgens).

Women are currently being treated according to their presenting clinical symptoms, including irregular menses, hirsutism and infertility.^{1,2,5}

Irregular Menses

A combined oral contraceptive pill is commonly used to regulate the menses. By both increasing the levels of sex hormone binding globulin (SHBG) and decreasing androgen secretion, this can reduce elevated free testosterone activity. The combined pill worsens insulin resistance and if the patient falls into the categories of being overweight or obese, this therapy is relatively contraindicated.^{1,2}

Hirsutism

Hirsutism is addressed with the administration of the anti-androgens cyproterone acetate or spironolactone. The action of these drugs is to inhibit the binding of dihydrotestosterone (DHT) to the receptors at the hair follicle site.⁶

Infertility

Clomifene citrate is suggested to women with PCOS who are diagnosed with fertility challenges. This drug induces ovulation and does increase risk of multiple pregnancies.⁶ It acts by inhibiting the estrogen negative feedback at the hypothalamus, thus enhancing the pituitary's production of FSH.

Other Pharmaceutical Medications

Other pharmaceutical medications which can be prescribed for PCOS include medroprogesterone acetate, gonadotrophin releasing hormone agonists, glucocorticoids, ketoconazole, flutamide, finasteride and metformin.

Overview of Botanical Protocol

Strong evidence supports the current hypothesis that the underlying cause of PCOS is due to insulin resistance (a decreased peripheral sensitivity to insulin), hence managing this aspect becomes the most important feature for the phytotherapist. The exact mechanisms for insulin resistance are not yet known within the conventional medical community, however the holistic practitioner finds that insulin resistance has a high correlation to a diet high in refined carbohydrates coupled with a poor adrenal glycemic counterbalance. As the HPA axis becomes weakened (as a result of chronic stress), insulin sensitivity becomes heightened, adversely affecting the ovaries and thyroid. Elevated insulin and insulin-like growth factor have an effect in stimulating androgen production from the adipose tissue, ovaries and adrenals. Under chronic stress, excess cortisol is produced from the adrenal glands, triggering the release of elevated levels of prolactin and a

sympathetic nervous system response.⁴ Prolactin has an inhibitory effect on the production of FSH and elevates the production of LH, worsening the scenario for women with PCOS. It is essential that the adrenals are well supported at a functional level with herbal adrenal tonics such as *Glycyrrhiza glabra* and supported by adaptogens such as *Withania somnifera*.

The first step in restoring ovarian function and a normal menstrual cycle in a PCOS patient is to break the pattern of hyperinsulinemia with a combination of diet and lifestyle strategies. Implementing a low refined carbohydrate diet and exercise is essential for a truly successful protocol.

Primary Herbs

Paeonia lactiflora (White peony)
Gymnema sylvestre (Gymnema)
Tribulus terrestris (Tribulus)
Vitex agnus-castus (Chaste tree)
Caulophyllum thalictroides (Blue cohosh)

***Paeonia lactiflora* (White peony)**

Paeonia lactiflora has been used for gynecological conditions by both Chinese and Western herbalists, and is used by Western herbalists for PCOS, hyperprolactinemia, endometriosis, ovarian failure and androgen excess. White peony has been shown to positively influence low progesterone, reduce elevated androgens (testosterone) and acts to modulate estrogen and prolactin.⁷ *In vitro*, the active constituent paeoniflorin has been shown to affect the ovarian follicle by its action on the aromatase enzyme.⁸ Aromatase is important for follicle maturation, ovulation and corpus luteum function, steroid hormone synthesis and the regulation of the conversion of androgens to estrogens. The biofeedback in the pituitary and hypothalamus rely on aromatase to regulate prolactin and GnRH. The daily dose for White peony is 4.5 to 9 mL of a 1:2 dried plant extract.⁹

The traditional Chinese/Kanpo formula known as Shakuyaku-Kanzo-To or TJ-68, which is a decoction of *Glycyrrhiza glabra* and *Paeonia lactiflora*, has been the subject of a number of clinical trials, all of which demonstrate activity in the hormonal regulation of androgens. In one trial involving eight women with hyperandrogenism and oligomenorrhea, the formula was given for 2 to 8 weeks. This combination regulated the LH to FSH ratio. Over this period of time, serum testosterone levels decreased to less than 50 ng/dL and this resulted in seven of the eight women ovulating regularly.¹⁰

Another trial involved 20 women diagnosed with PCOS. The formula was successful in lowering testosterone in 90% of the women, of which 25% went on to conceive.¹¹ It is suggested that it acts directly on the ovary, increasing the activity of aromatase, which promotes the synthesis of

estradiol from testosterone, thus lowering serum testosterone levels. It also seems to regulate the LH to FSH ratio.¹²

***Gymnema sylvestre* (Gymnema)**

Gymnema is a traditional Ayurvedic herb used as an antidiabetic, hypoglycemic, lipid lowering agent and to support weight reduction. Gymnema possibly has a trophorestorative action of the beta cells of the pancreas.¹³ The plant part used as medicine is the leaf. Gymnema is well indicated for PCOS, due to its insulin modulating activity and the added benefits of reducing the elevated triglycerides associated with PCOS. Key constituents of Gymnema include saponins, especially the gymnemic acids. Gymnemic acid suppresses the sweet taste on the taste buds, so if taken before food masks the sweet sensation. Gymnema has demonstrated hypoglycemic activity in experimental models of diabetes and regulated blood sugar in hyperglycemia. The mechanism of action also includes the inhibition of glucose absorption in the intestine. The daily dose of Gymnema is 3.5 to 11 mL of 1:1 liquid extract.^{9,14} Since conventional medical models are focussing on pharmaceutical agents such as metformin to control PCOS, Gymnema may prove to be one of the most significant herbs in the treatment of the underlying factor of insulin resistance.

***Tribulus terrestris* (Tribulus)**

Tribulus is an endemic weed to many regions of the world, such as the Mediterranean, India, China, South Africa and Australia and is commonly known as puncture vine. The aerial parts, particularly the leaf, are used for medicinal purposes in the Western tradition. As a result of Bulgarian research, Tribulus has become a popular herb for the treatment of female and male endocrine disorders.¹⁵ It acts as a general tonic, aphrodisiac, estrogen modulator and androgen modulator and is used to restore vitality, libido and reduce the physiological effects of stress.^{9,11}

The Bulgarian research has identified a unique steroidal saponin class known as furostanol saponins, and extracts are standardized to contain at least 45% of these saponins, calculated as protodioscin. The leaf is noted to be higher in these unique saponins rather than the fruit or root. Other active constituents include phytosterols and spirostanol glycosides.

The tonic activities of Tribulus have been shown to act by intensifying protein synthesis and enhancing the activity of enzymes associated with energy metabolism. It increased iron absorption from the small intestines and inhibited lipid peroxidation during stress. This leads to more muscle strength and improved endurance and stamina.⁹

To ensure the desired clinical results, it is recommended to use only the Bulgarian grown Tribulus standardized to 40% furostanol saponins. It is not interchangeable with the

Chinese or Indian Tribulus. The daily dose of Tribulus corresponds to extracts containing furostanol saponins as protodioscin at 300 mg to 400 mg per day. In PCOS it is best used on days 5 to 14 of the menstrual cycle to restore menstrual regularity. For more information on Tribulus, see the forthcoming review which will be published in next month's *Townsend Letter*.

***Vitex agnus-castus* (Chaste tree, Vitex)**

Vitex is beneficial for ovulatory factors associated with PCOS, in particular it has been shown to downregulate the production of excess prolactin, a condition known as hyperprolactinemia.¹⁶ Vitex is also postulated as having antiandrogenic properties.¹⁶ Hyperprolactinemia is related to adrenal stress and hyperinsulinemia in PCOS. It is well documented that the active constituents in Vitex demonstrate a dopaminergic activity and dopamine inhibits the production of prolactin. The dopaminergic compounds in Vitex have been identified as the diterpene, including rotundifuran and 6 β ,7 β -diacetoxy-13-hydroxy-labda-8,14-diene. However, recent research is pointing to other phytochemicals which may have this activity.¹⁷ Other constituents of Vitex include essential oils, flavonoids (such as casticin) and iridoid glycosides (including aucubin and agnuside).^{9,14}

Hyperprolactinemia, or the more subtle condition of latent hyperprolactinemia, are amongst the most frequent causes for cyclical disorders, including corpus luteal insufficiency. This can lead to premenstrual syndrome (PMS) and progesterone deficiency, secondary amenorrhea and premenstrual mastalgia.¹⁸ In an uncontrolled study, Vitex reduced elevated prolactin levels in 80% of 34 women with hyperprolactinemia at a dosage of 30 to 40 mg per day for 1 month and improved symptoms of a variety of menstrual disorders, including secondary amenorrhoea, cystic hyperplasia of the endometrium, deficient corpus luteum function, metrorrhagia, polymenorrhea and oligomenorrhea.⁹

Vitex reduced the thyroxin releasing hormone (TRH)-induced prolactin release (essentially a pituitary-thyroid axis problem), normalized shortened luteal phases, corrected luteal phase progesterone deficiencies and reduced PMS symptoms in women with luteal phase defects due to latent hyperprolactinemia.⁹

Vitex should be considered first line botanical therapy for hyperprolactinemia and given for the duration of at least 3 to 6 months. In herbal writings Vitex is often attributed to increasing LH, which is not desirable in PCOS. However, clinical experience has shown that it is valuable in PCOS, especially when combined with other herbs, probably because of its action in reducing prolactin. The daily dose of Vitex is 1 to 4 mL of a 1:2 dried plant tincture or 500 to 1000 mg of dried berries daily.⁹ It is best taken as a

single dose in the morning.⁹ In PCOS it is best combined with Tribulus and White peony.

***Caulophyllum thalictroides* (Blue cohosh)**

Caulophyllum thalictroides is known by the common name of blue cohosh and is native to North America. Within traditional use among the Native North Americans it was used for women as a remedy for amenorrhea and profuse menstruation, both of which are common features of PCOS. It is particularly useful to bring on the menses in PCOS. It has action as a uterine and ovarian tonic and pelvic anti-inflammatory. The known constituents of *Caulophyllum thalictroides* root include glycosides, caulosaponin and caulophyllosaponin, which are known to stimulate the uterus. Other identified constituents include N-methylcystine, taspine and thalictroidine.⁹ The daily dose is 1.5 to 3 mL of 1:2 dried plant extract.⁹

Sample PCOS Formula

<i>Vitex agnus-castus</i>	1:2	12.5 mL
<i>Glycyrrhiza glabra</i>	1:1	12.5 mL
<i>Paeonia lactiflora</i>	1:2	25 mL
<i>Gymnema sylvestre</i>	1:1	25 mL
<i>Schisandra chinensis</i>	1:2	<u>25 mL</u> 100 mL

Dose: 15 mL per day or 5 mL three times daily

In a case of a PCOS patient with amenorrhea, include *Caulophyllum thalictroides* at a dose of 2 mL per day to help induce the menses.

When a cycle has been initiated, change to Tribulus concentrated extract, equivalent to furostanol saponins (as protodioscin) 300 to 400 mg per day on days 5 to 14 of the cycle to ensure cyclic regularity.

Dietary Modification

A review of the extensive literature specific to lifestyle factors in PCOS demonstrates that an essential treatment strategy for ameliorating the symptoms of PCOS and resolving the underlying metabolic derangements is the implementation of a low carbohydrate diet. This will tightly control blood sugar levels and resultant insulin production. High levels of insulin result in high levels of triglycerides and low levels of high density lipoproteins, which puts these patients into a high cardiovascular disease risk category. Modulating the diet not only helps the female endocrine cycle, but also serves as preventative medicine against these cardiovascular risk factors. As the insulin levels normalize, this will also improve circulating levels of SHBG, therefore limiting the problematic effects of free androgens on the menstrual cycle.^{2,6}

Women with PCOS are urged to lose 5 to 10% body weight using a moderate protein, low refined carbohydrate diet. When this approach was taken in one clinical trial, 10 of the 11 subjects resumed a normal cycle within 10.5 months.² In a similar study, such weight loss restored ovulation in 60 out of 67 previously anovulatory women.³ The dietary profile should include approximately 30% good quality fats, 40% protein and 30% complex carbohydrates.^{1,2,19} Literature suggests establishing an energy efficient diet of 1000 to 1500 kcal per day. It is recommended to avoid alcohol, caffeine, smoking and psychosocial stressors. Gymnema is helpful in reducing carbohydrate and sugar cravings, and therefore improving compliance with dietary changes.⁹

Exercise

Implementing an exercise regime of approximately 30 minutes per day will assist weight loss and improve the endocrine regulation of stress.

Case History

Case Overview

Female patient aged 34 presented with irregular menses and was considering attempting to fall pregnant. She had been diagnosed with PCOS for the past 2 years. Up until 6 months prior to her consultation, she had taken the oral contraceptive in combination with Levoxyll, but suffered side effects of heightened emotional lability from these drugs.

Her menstrual cycle varied in length anywhere from 50 to 70 days and she experienced mid-abdominal cramping for 24 hours prior to the onset of her menses. The flow was medium to light and lasted for 4 to 5 days, dark red in color, starting with brown spotting for 12 to 18 hours. She had occasional menstrual clots, stringy and lumpy in nature.

Her skin was affected badly by the PCOS and she experienced painful, deep cystic acne on her face, chest and back, which was worse for up to a week before the onset of each period. She had taken two courses of isotretinoin (Accutane) within the past 5 years and regularly used a tetracycline for treatment of her acne. Breast tenderness was an uncomfortable premenstrual feature.

She had gained 23 pounds over the past 3 years, which she had difficulty losing, despite exercise on a regular basis. She did however have a high carbohydrate diet and craved sugar intensely.

She was a shift worker in a high stress and responsibility occupation and fatigue was a daily experience.

She was taking prescribed thyroid hormone (thyroxine) for Hashimoto's thyroiditis, diagnosed 4 years prior. At the same time she was diagnosed as having secondary osteoporosis. Recent evaluation showed her spinal density indicated osteopenia, her femoral density indicated osteoporosis and total hip density indicated severe osteopenia.

Additional Assessment

Hormonal evaluation showed a typical pattern of a 2:1 LH to FSH ratio, with elevated testosterone and hyperlipidemia.

Treatment Protocol

<i>Vitex agnus-castus</i>	1:2	12.5 mL
<i>Glycyrrhiza glabra</i>	1:1	12.5 mL
<i>Paeonia lactiflora</i>	1:2	20 mL
<i>Gymnema sylvestre</i>	1:1	20 mL
<i>Echinacea spp.</i> root	1:2	10 mL
<i>Schisandra chinensis</i>	1:2	<u>20 mL</u> 100 mL

Dose: 8 mL twice daily

Additionally:

- Tribulus concentrated extract, equivalent to furostanol saponins (as protodioscin) 300 to 400 mg per day on days 5 to 14 of the cycle to ensure cyclic regularity.
- *Fucus vesiculosus* 1:1, 10 mL twice daily.

Rationale

Vitex agnus-castus was indicated for the hormonal imbalance and hyperprolactinemia, often resulting in the symptom of premenstrual breast tenderness. A combination of *Glycyrrhiza glabra* and *Paeonia lactiflora* were included into the formula to mimic the synergy of these plants in TJ-68 to reduce elevated testosterone and induce ovulation. *Gymnema sylvestre* was included in the formula to treat the insulin resistance and hyperlipidemia and assist with reducing associated carbohydrate cravings. *Echinacea spp.* root was an important inclusion for the autoimmune mediated hypothyroid condition. *Echinacea* serves as an immune modulator in this case. *Schisandra chinensis* was included in the formula to provide liver support, in particular to improve the liver's ability to conjugate sex hormones, and assist in reducing the circulating levels of testosterone and estrogen. *Tribulus* was selected to ensure a healthy follicular phase of the cycle and as an androgen modulator. *Fucus vesiculosus* was indicated for thyroid support as a plant source of iodine and is traditionally recommended by herbalists to assist with weight loss associated with hypothyroidism.

Conclusion of Care

After 5 months on the herbal protocol, the patient's cycle had regulated to a 32 day cycle, with a consistent 15 day

follicular phase and a 17 day luteal phase. Problematic symptoms such as mastalgia, acne and hirsutism diminished significantly during the 5 month program. The lipid profile has improved to within normal ranges, and with the inclusion of the combined regimen of Gymnema, dietary modification (low carbohydrate diet) and exercise, she lost a total of 12% body weight in the 5 months. She went on to begin a full preconception health care program and fell pregnant in her second month.

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