Polycystic Ovary Syndrome: Current Understanding and Treatment Alternatives

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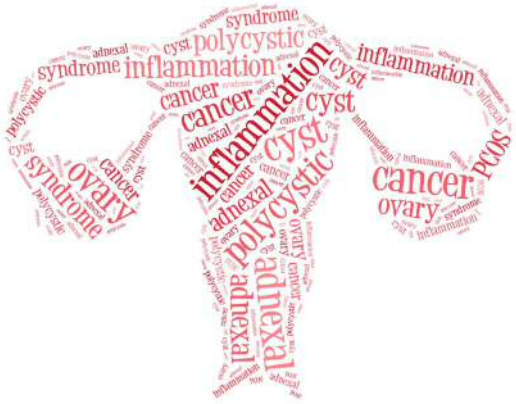

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Polycystic ovary syndrome (PCOS) is a relatively common and frequently misunderstood condition with variable clinical presentation. Its key features are irregular or absent menses often followed by episodic heavy and prolonged menses; infertility; central obesity; androgenization (acne, male-pattern hair loss, and hirsutism); and multiple ovarian cysts. It is estimated to affect 5–10% of women and is thought to have both genetic and environmental roots.

Most women with PCOS will present with only two or three of the clinical features of PCOS. Approximately 70% will have missed periods (oligomenorrhea) or lack of periods (amenorrhea). Obesity is present in 70%. Hirsutism to a varying degree is present in roughly 75%, and ovarian cysts—unilateral or bilateral—are present in 90% (Azziz et al, 2004; Clayton et al, 1992; Huang et al, 2010; Farquhar et al, 1994; Legro, 2005). Ethnicity plays a role in the presentation of PCOS. For example, women of Asian descent are less likely to have hirsutism (Carmina et al, 1992). The variability in presentation of PCOS reflects heterogeneous causative factors. Thus, the approach for each woman needs to be individualized based on her particular presenting symptoms and laboratory findings.

Pathophysiology of PCOS

In selecting an appropriate botanical prescription for a woman with PCOS, it is important to understand the pathophysiology behind the symptoms. Research continues to shed light on the more common physiologic and genetic aberrations leading to PCOS. Genetic contributions to PCOS are evidenced by familial clustering of cases and stronger concordance in monozygotic twins (Diamanti-Kandarakis et al, 2006).

The most common underlying cause of PCOS is insulin resistance, which is observed in both normal weight and overweight women with PCOS. Insulin resistance occurs at some level in 50–80% of PCOS patients (Dunaif, 1997). Insulin resistance can occur through multiple mechanisms including genetic predisposition and lifestyle impact. Obesity has a well-known correlation with insulin resistance and plays an increasing role in PCOS given the current obesity epidemic in the United States and much of the developed world. Overweight and obese women with PCOS are more likely to have glucose intolerance than normal weight women with the syndrome. However, even normal weight women with PCOS tend to have altered body fat distribution with more central (visceral) obesity that is associated with elevated insulin levels and insulin resistance (Douchi et al, 1995).

Insulin resistance in at least 50% of PCOS women appears to be related to excessive serine phosphorylation of the insulin receptor, resulting in decreased glucose uptake by muscle cells (Dunaif, 1995). The resultant increase in circulating insulin then appears to augment ovarian and adrenal steroidogenesis and pituitary LH release directly through the insulin receptor (Douchi et al, 1995; Dunaif, 1995). Serine phosphorylation also appears to modulate the activity of the key regulatory enzyme of androgen biosynthesis P450c17 (Dunaif, 1995), shedding light on the co-occurrence of insulin resistance and androgenization commonly seen in the syndrome.

Another mechanism for insulin resistance in PCOS has recently been discovered and is linked to an increase in microRNA (Chen et al, 2013), resulting in decreased GLUT-4 activity. GLUT-4 is instrumental

in fat cell responsiveness to insulin. Thus, the GLUT-4 deficiency results in elevated glucose levels leading to a compensatory increase in circulating insulin levels (Chen et al, 2013).

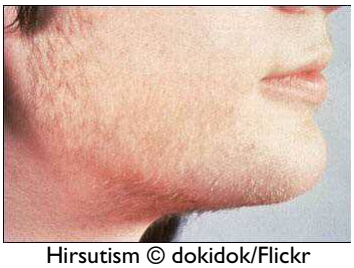
The question is raised as to why the ovaries are so sensitive to insulin when the rest of the body's cells are resistant to it. Research has demonstrated that insulin action in the ovaries is mediated by inositol glycan at the post receptor level, and not by tyrosine–kinase cascade. Thus, the high circulating insulin levels have more direct influence on the ovaries than on other tissues in the body (Nestler et al, 1998).

Insulin also has a direct impact on the pituitary gland. The elevated insulin level found in insulin resistance increases the pulse frequency of the gonadotropins which results in LH over FSH dominance, increased ovarian androgen production, decreased follicular maturation, and decreased sex-hormone-binding. In a positive feedback loop, increased androgens increase insulin resistance (Dunaif, 1997).

Estrogen dominance and unopposed estrogen are issues in PCOS that pose additional health risks. Higher levels of estrone and estradiol are derived from increased aromatase activity in the excess visceral adipose tissue. Increased estrogen feeds back to the pituitary to reduce follicle stimulating hormone (FSH), resulting in arrest of ovarian follicle development (the "cysts" seen in the ovaries are actually arrested follicles). Arrested follicles cause anovulation, with the subsequent failure of ovarian progesterone production that follows normal ovulation. Early on, prolonged unopposed estrogen produces episodes of irregular, heavy, prolonged bleeding (dysfunctional uterine bleeding). Over time there is an elevated risk for uterine hyperplasia and cancer due to persistently unopposed estrogen.

Another route to PCOS is postulated to be through a primary disturbance in androgen production. Increased androgens alone can contribute to the cascade of PCOS through increasing visceral fat (Elbers et al, 1997), leading to insulin resistance, elevated circulating insulin levels, and ovarian dysfunction. In normal ovarian physiology, androgens produced by LH-stimulated theca cells undergo aromatization to estrogens by FSH-stimulated granulosa aromatase. As aromatase activity increases and estrogen levels increase, ovulation usually follows. In some PCOS patients, the ratio of follicular androstenedione (theca cell androgen) to estradiol is elevated and a mutation in the P450 aromatase gene has been found to be a cause of this shift (Conte et al, 1994).

Elevated prolactin levels have been shown to correlate with PCOS. While very high prolactin levels are usually caused by a prolactin-secreting pituitary tumor, mildly elevated prolactin levels can be triggered by stress. Increased prolactin levels can also be caused by the persistently elevated estradiol levels seen in PCOS. An overly sensitive pituitary has been implicated as women with PCOS have been shown to have a more vigorous and/or prolonged prolactin response to infusions of TRH (thyroid releasing hormone). PCOS is also associated with a more vigorous prolactin response to dopamine blockers (Falaschi et al, 1980). Prolactin promotes insulin resistance, so again the final common pathway is in part through the insulin receptors on the ovaries. In addition, elevated prolactin levels are known to promote hirsutism.


Hirsutism © dokidok/Flickr

TRH infusions in women with PCOS compared to normal controls have also been shown to produce elevated concentrations of LH, testosterone, and androstenedione, and 24-hour urinary estrogen excretion (Milewicz, 1984). TRH tends to rise during times of stress (Milewicz, 1984).

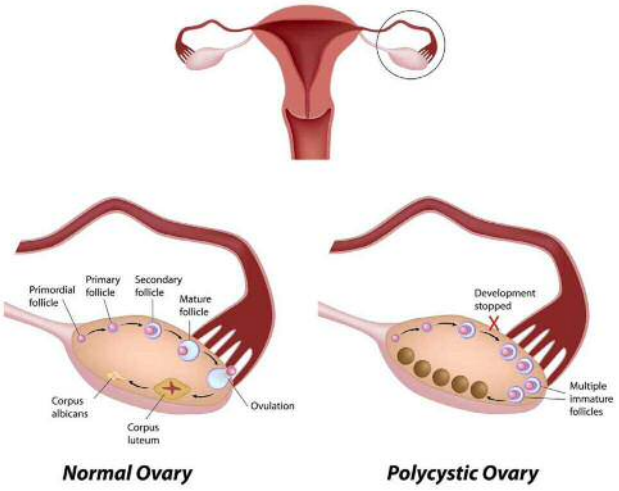
PCOS has also been shown to involve increased inflammation and oxidation, raising risks for subsequent cardiovascular disease and cancer (Sathyapalan and Atkin, 2010; Fukuoka et al, 1992; Murri et al, 2013).

Differentiating PCOS from other medical problems

Each clinical feature of PCOS must be run past a list of alternative diagnostic possibilities. Amenorrhea and oligomenorrhea can be caused by pregnancy, a prolactin-secreting pituitary tumor, primary ovarian failure, early menopause, stress, rapid weight gain, low body mass index (BMI), hyperathleticism, and several other less common physiologic and hormonal disturbances. Heavy irregular bleeding may be caused by

endometrial cancer, cervical cancer, fibroids, adenomyosis, endometrial polyps, and clotting disorders such as Von Willebrand's disease. Hirsutism can be caused by primary adrenal hyperplasia (a congenital disorder), androgen-secreting tumors on the adrenal glands and ovaries, Cushing syndrome, hypersensitivity of hair follicles to testosterone, a prolactin-secreting adenoma, and several pharmaceutical drugs.

The ovarian "cysts" of PCOS are unique in that they appear as multiple (10–20) small cysts, often forming a bubbly ring around the ovary on ultrasound. These cysts are easily distinguishable on ultrasound from benign solitary ovarian cysts that occur in up to 20% of women and from complex cysts and ovarian cancer that are also usually solitary. The numerous PCOS cysts are actually ovarian follicles that have been halted in their monthly march toward ovulation. These cysts develop a "thick skin" (thecation) under the stimulation of luteinizing hormone (LH).



Polycystic ovary © EIMC

Diagnosing PCOS

When a woman presents with any two features of PCOS, further evaluation for PCOS is warranted. There are a variety of definitions of PCOS but the two most accepted ones are:

NIH consensus: A woman should have all of the following: oligoovulation, signs of androgen excess (clinical or biochemical), other entities are excluded that would cause polycystic ovaries.

Rotterdam consensus: Any 2 of the following: oligoovulation and/or anovulation, excess androgen activity, polycystic ovaries (12 or more 5–7mm follicles) by ultrasound (Hart et al, 2004).

By the Rotterdam criteria, a woman can have one of four PCOS syndromes:

PO: polycystic ovaries with anovulation

PH: polycystic ovaries with hyperandrogenism and normal ovulation

PHO: polycystic ovaries with hyperandrogenism and anovulation

HO: hyperandrogenism and anovulation with normal ovaries on ultrasound

Research has shown that women with the PO syndrome do not show a tendency toward insulin resistance and metabolic syndrome in contrast to women who have all three features of PCOS (Barber, 2007).

Laboratory tests

Serum LH and LH/FSH ratio are significantly higher in women with PCOS, but these tests are abnormal in only about 40% of patients with PCOS. Mean serum total testosterone concentration is significantly higher in about 70% of women with PCOS. Androstenedione is significantly higher in about 50% of women with PCOS. When testing for all of the above, an abnormality will be detected in about 80% of women with PCOS. If serum testosterone levels exceed 150ng/dL, a virilizing tumor of the ovaries should be ruled out with pelvic ultrasound (Robinson et al, 1992).

Other laboratory tests that may be indicative of other diagnoses or of co-morbid conditions include serum prolactin, HCG, fasting glucose and insulin, lipid profile, DHEA-S, 17-hydroxyprogesterone, and dexamethasone suppression test. DHEA-S levels greater than 700 suggest adrenal dysfunction warranting adrenal imaging.

Ultrasounds will identify polycystic ovaries, typically bilaterally enlarged ovaries with more than eight follicles per ovary, with follicles less than 10mm in diameter. More than 90% of women with PCOS have this finding, which also occurs in 25% of normal women. Other common laboratory features are elevated LH, estrone, and testosterone in the presence of normal estradiol (in idiopathic hyperprolactinemia, estradiol levels are suppressed). 24 hour urinary estrogen levels are increased in PCOS, particularly in response to a bolus of TRH (often triggered by stress).

Treating PCOS

Women who seek treatment for PCOS are primarily concerned with correcting abnormal menses (particularly when it evolves into dysfunctional uterine bleeding), infertility, weight gain, hirsutism, and acne. Health care providers have additional preventive interests with regard to associated increased risks for endometrial cancer and cardiovascular disease from hyperinsulinism (Mather, 2000). The risk of endometrial cancer is three times higher in women with PCOS (Mayo Clinic, 2011). There is also conflicting evidence for a three-fold increased risk for breast cancer in the postmenopausal years with chronic anovulation (González, 1983).

Conventional treatment for PCOS includes the use of behavior modification directed at weight reduction and glucose regulation, pharmacologic therapy directed at presenting complaints and prevention of complications, and rarely surgical treatment of the ovaries. Examples of pharmaceuticals include metformin to address insulin resistance, clomiphene to stimulate ovulation for women seeking pregnancy, bromocriptine or cabergoline to reduce prolactin, progesterone to regulate menses and reduce risk of endometrial cancer, and spironolactone to block androgens (Lucidi, 2011). Combined estrogen/progesterone birth control pills are commonly used to regulate cycles, reduce acne and hirsutism, and reduce risks to the endometrium. Vitamin D deficiency may play a role in development of metabolic syndrome (Thomson et al, 2012), so Vitamin D supplementation should be provided to women with a deficiency.

Dietary measures should focus on weight loss and reduction in circulating insulin levels through carbohydrate restriction, particularly refined carbohydrates. A 2013 scientific review showed improvement in pregnancy rates, menstrual regularity, hyperandrogenism, and quality of life with weight loss regardless of dietary regimen (Moran, 2013). As a dietary supplement, myo-inositol has been shown to be effective in treatment of PCOS (Unfer et al, 2012).

Tincture blend © EIMC

The botanical approach to a woman with PCOS should take into consideration the unique pathophysiology of each woman, addressing as warranted:

1) Insulin resistance
2) Elevated ovarian and adrenal androgens
3) Elevated estrogen
4) Elevated LH
5) Insufficient progesterone
6) Elevated prolactin
7) Lactotroph hypersensitivity to TRH
8) Anovulation
9) Inflammation
10) Oxidation
11) Underlying stress
12) Obesity and metabolic syndrome

In addition, targeting frequently associated co-morbidities such as fatty liver, hypertension, depression with anxiety (Barry et al, 2011), cardiovascular disease, and dyslipidemia is warranted.
Examples:

Case 1

A 35-year-old woman presents with acne, central obesity, diminishing menstrual regularity since the birth of her third child four years ago. She gained a lot of weight with her last pregnancy and has been unable to lose the excess 30 lbs/2 kg. Her last menstrual period was five months ago. Ultrasound shows 16 small cysts on the periphery of her ovaries. LH/FSH ratio is moderately elevated. Testosterone is upper limits of normal. Pregnancy test is negative.

Analysis

Her problem is likely due to the excess weight gain from her last pregnancy, with the excess weight producing metabolic syndrome and increased circulating insulin levels, leading to ovarian dysfunction. She now has anovulation and unopposed estrogen, placing her at immediate risk of dysfunctional uterine bleeding and at long-term risk of endometrial cancer. Elevated insulin levels are producing hyperandrogenic output from the ovaries causing acne. Due to the increased insulin levels, she is also at long-term risk of hypertension and cardiovascular disease.

Treatment should be directed at a life-long, low-glycemic or other weight-reduction diet and an interval exercise program to promote weight reduction. Bo-

tanical support with herbs shown to reverse metabolic syndrome would include herbs like Cinnamon (*Cinnamomum zeylanicum*) and Lemon Balm (*Melissa officinalis*)(Wang et al, 2007; Weidner et al, 2014). Progesterogenic plants such as Chaste Tree (*Vitex agnes castus*) would help support the endometrium. Chaste Tree would also be essential in promoting ovulation via prolactin reduction and reducing excess estrogen levels via FSH antagonism (Van Die et al, 2013; Grant and Ramasamy, 2012). In addition, antioxidant and anti-inflammatory herbs, Milk Thistle (*Silybum marianum*)(for fatty liver)(Milic et al, 2013), and anxiolytics such as Lavender (*Lavandula angustifolia*), Bergamot (*Citrus bergamia*), and Lemon Balm would be useful to address secondary complications of the disorder (Toda and Morimoto, 2008; Bagetta et al, 2010; Alramadhan et al, 2012).

Vitex chaste tree © EIMC

Case 2

A 24-year-old woman presents with gradually increasing hair growth on her chin, central chest, and lower abdomen since menarche at age 12. She continues to have mild to moderate acne. In the past twelve months her menses have become increasingly irregular and her last menstrual period occurred about four months ago. She has a normal body mass index but noted increased waist:hip ratio (signifying visceral fat accumulation). Her serum testosterone level and androstenedione level are moderately elevated. DHEA-S and 17-OH-progesterone and prolactin levels are normal. Ultrasound shows numerous 5–7mm cysts on both ovaries.

Analysis

Her problem is likely a hereditary ovarian defect resulting in elevated ovarian androgen production (decreased aromatization or increased insulin sensitivity). She is less likely to have excess estrogen levels or excess insulin levels. Focus should be on reducing her androgens and improving aromatization. Herbs such as Licorice (*Glycyrrhiza glabra*) to balance aromatization of estrogens and decrease ovarian androgen production would be the mainstay for this woman (Sil et al, 2013; Grant and Ramasamy, 2012). Myo-insitol may also be appropriate in this case (Unfer et al, 2012). Saw Palmetto (*Serenoa repens*) and

Herbs that may be useful in the treatment of PCOS	
Chaste Tree (*Vitex agnus castus*) berry	Prolactin modulator, reduces TRH-stimulated prolactin secretion, increases mid-luteal progesterone level (Van Die et al, 2013; Grant and Ramasamy, 2012)
Licorice (*Glycyrrhiza glabra*) root	Reduces testosterone, reduces insulin resistance, anti-inflammatory (Sil et al, 2013; Grant and Ramasamy, 2012)
African Prune (*Pygeum africanum*) bark	5-alpha reductase inhibitor, anti-inflammatory (Schleich et al, 2006)
Lemon Balm (*Melissa officinalis*) leaf	Reduces insulin resistance, anxiolytic (Weidner et al, 2014; Elham et al, 2012)
Cinnamon (*Cinnamomum zeylanicum*) bark	Reduces insulin resistance, anti-inflammatory (Wang et al, 2007)
Lavender (Lavandula angustifolia) flower	Stress relief, anxiolytic (Toda and Morimoto, 2008; Elham et al, 2012)
Bergamot (*Citrus bergamia*) peel	Mood enhancing, anti-inflammatory, antioxidant (Bagetta et al, 2010)
Spearmint (*Mentha spicata*) leaf	Antiandrogenic, anti-inflammatory (Grant and Ramasamy, 2012; Grant, 2010)
Chamomile (*Matricaria chamomilla*) flower	Anti-inflammatory, normalizes LH, increases dominant follicles (Farideh et al, 2010)
Saw Palmetto (*Serenoa repens*) berry	5-alpha reductase inhibitor (Grant and Ramasamy, 2012; Abe et al, 2009)
Milk Thistle (*Silybum marianum*, *Carduus marianus*) seed	Hepatoprotective, regenerative, detoxifying, antioxidant, anti-inflammatory (Milic et al, 2013)

Sample phytotherapeutic PCOS treatment	
Mother tincture blend	
Chaste Tree mother tincture	60 cc/ml
Licorice mother tincture	60 cc/ml
African Prune mother tincture	60 cc/ml
Lemon Balm (Melissa) mother tincture	60 cc/ml
Cinnamon Bark essential oil	3 cc/ml
Lavender essential oil	3 cc/ml
Bergamot essential oil	3 cc/ml
Blend all of the above together in an 8 oz/240 ml glass bottle. Shake well before use. Take 2 cc morning and evening diluted in a small glass of water.	
Herbal tea	
Spearmint leaf bulk herb	8 oz/225 gm
Chamomile flower bulk herb	8 oz/225 gm
Mix tea well and store in an airtight container. Pour 1 liter of boiling water over 4 tablespoons tea. Cover, steep 15 minutes, strain, and drink throughout the day each day.	
Herbal extract capsules	
Saw Palmetto	Milk Thistle
Take 1–2 capsules of each morning and evening.	
Note: This sample phytotherapeutic treatment is intended to be used under the supervision of a qualified healthcare professional. Optimal results are achieved when treatment plans are customized to each patient.	

African Prune (*Pygeum africanum*) may also be useful for the hirsutism via reduction of 5-alpha reductase (Grant and Ramasamy, 2012; Schleich et al, 2006; Abe et al, 2009). In addition, she would benefit from the herbs noted in Case 1 to prevent secondary complications. ☙

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