

A Detailed Study on Poly Cystic Ovarian Syndrome and It's Treatment With Natural Products

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is a common disorder affecting 4% to 12% of women of reproductive age. The common symptoms of PCOS are irregular menstrual cycles, anovulation, infertility, hirsutism, hyperandrogenism, acne, the scalp hair thinning, functional ovarian hyperandrogenism, peripheral insulin resistance, hyperinsulinemia, and obesity. In this review the signs and symptoms, reasons for elevated levels of hormones and management of PCOS with allopathic medications like Clomiphene citrate, Tamoxifen, Metformin etc and natural remedies using Liquorice, Aloe vera, Cinnamon, N-acetyl cysteine etc are discussed in brief.

Key words: Hyperandrogenism, Hyperinsulinemia, Tamoxifen, Metformin, Liquorice, Aloe vera

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is sometimes called Stein-Leventhal Syndrome after the two doctors who first described it in 1935.¹ It is an extremely common disorder affecting 4% to 12% of women of reproductive age.²⁻³ A PCOS patient's ovaries have more than ten follicles visible on ultrasound. The common symptoms like irregular menstrual cycles, anovulation, infertility, hirsutism, hyperandrogenism, acne, the scalp hair thinning and functional ovarian hyperandrogenism are found in 70% of the patients with PCOS. PCOS is also associated with peripheral insulin resistance and hyperinsulinemia, and obesity amplifies the degree of both these abnormalities.⁴ The presence of enlarged polycystic ovaries suggests that the ovaries are the primary sites of abnormality in PCOS. The etiology of PCOS remains unclear; however, several studies have suggested that insulin plays the basic pathologic role along with a genetic component to the syndrome.⁵⁻⁷ As the condition progresses it may become associated with dysfunctional uterine bleeding, obesity, Type 2 diabetes, endometrial cancer, high cholesterol and cardiovascular disease.¹¹⁻¹²

Traditional herbal medicines are naturally occurring substances with minimal or no industrial processing that have been used to treat various illnesses. Traditional medicines have established preventive, curative and rehabilitative role.⁸⁻¹⁰ Benefit of herbal therapy compared to conventional therapy is that it is safe with lesser side effects and presence of multiple active compounds in medicinal herbs altogether provides a potentiating effect.¹³⁻¹⁴

In this review, the treatment of different aspects of PCOS is discussed, with a particular emphasis on the natural products.

The Polycystic Ovary: In comparison to the normal ovary, the polycystic ovary is larger, has more follicles and has a particularly dense centre – the stroma which is where testosterone is made. On average, the normal ovary contains five follicles and is about the size of a walnut. The polycystic ovary contains 10 or more follicles, usually these are small follicles measuring between 2 and 10 millimetres in diameter. The polycystic ovary is usually the size of a hen's egg but occasionally they may be the size of an orange. The increased size of the polycystic ovary is mainly due to an increased amount of stroma and not, as may be expected, because of the extra follicles or cysts. Usually, the follicles are too small to contribute much to the ovary size.¹⁵

Signs and symptoms of PCOS: The principal signs and symptoms of PCOS are:¹⁹

1) Irregular or absence of periods: Irregular and unpredictable uterine bleeding is the hallmark of PCOS. 85-90% women with PCOS have oligomenorrhoea while 30-40% present with amenorrhoea. These symptoms are clinical features of anovulation, but not all patients have anovulatory cycles as corpus luteum formation at the time of surgery has been found in approximately 16% of women with PCOS.¹⁶

2) Hirsutism, Acne, temporal balding (Androgen Excess): Approximately 80% of PCOS patients have excessive hair growth that usually has a male pattern. Prolonged exposure to high levels of circulating androgens may even cause temporal balding.¹⁷ Acne is commonly seen but severe form of androgen excess such as clitoromegaly is absent.

3) Weight gain or difficulty in losing weight: The onset of obesity has been correlated with the appearance of menstrual dysfunction. Patients usually have an android pattern of obesity.¹⁸ There are a variety of explanations why women with PCOS can be obese. Raised insulin levels

might, however, be a drive to the appetite centres of the brain. Weight gain results in higher insulin levels which in turn drives the ovary to make more testosterone. Thus, as women gain weight the concentration of testosterone in the blood rises. The cause of obesity may be uncertain but the fact of being overweight is clear.

4) Infertility: PCOS causes infertility by preventing ovulation.²⁰ Usually the egg is released 14 days before a period. If the periods are very irregular then ovulation may be unreliable or indeed - it may not take place at all.

5) Miscarriage: ¹⁵ Women with PCOS who also have a raised LH measurement are at an increased risk of miscarriage.

6) Changes in hormonal level:

Testosterone and other androgens: Ovary makes several androgens of which testosterone is the most prominent others include androstenedione and Dehydroepiandrosterone (DHEAS). The most typical feature of the polycystic ovary is that the stroma and theca cells make an excess of testosterone. The adrenal gland is another source of testosterone but the function of this gland is usually normal in women with PCOS.

The gonadotropins, LH and FSH: The monthly timing of the menstrual cycle is controlled by a complex balance of hormones from the hypothalamus and pituitary gland which is situated behind the eyes. The gonadotropins, LH and FSH are made by the pituitary gland. The Luteinising Hormone (LH) drives the theca cells of the ovary to make testosterone. Testosterone is then passed to the granulosa cell of the ovarian follicle where it is turned into oestrogen under the influence of follicle stimulating hormone (FSH). In one third of women with PCOS, the level of LH is raised and there is a rough association between this finding and a tendency to infertility. Concentrations of FSH seem to be decreased in women with PCOS.

Insulin and the metabolism: The main role of insulin in the body is in regulating the level of glucose in the blood. In some individuals, high concentrations of insulin are required in order to maintain normal glucose levels - insulin resistance. When insulin fails in this effort, diabetes occurs. Raised insulin concentrations have a side effect in the body of stimulating the ovary to produce more testosterone. About one third of lean women with PCOS have raised insulin levels and this proportion rises in those who are overweight. In obese women with PCOS about half have raised insulin levels and 10% have mild diabetes. Raised insulin levels are part of a metabolic syndrome which also includes high blood pressure and an adverse cholesterol profile - low HDL cholesterol and raised triglycerides.

Causes of PCOS: Following are few important causes of PCOS:²²

- 1) Genetic predisposition
- 2) Strong stimulation in adrenals in childhood
- 3) Raised insulin levels
- 4) Contraceptive pills
- 5) Hormonal imbalance
- 6) Stress

Reasons For Elevated Levels of Hormones in PCOS:

Androgen: Excess production of androgen is the most consistent biochemical feature seen in both women with PCOS and prenatally androgenized female rhesus monkeys, irrespective of the mode of clinical presentation or degree of menstrual cycle dysfunction.^{23, 24} Although the adrenal may contribute to excess testosterone circulating in women with PCOS,²⁵ the major source of excess androgen is the ovary.²⁶⁻²⁸ Both in vivo and in vitro studies of theca cell function show an exaggerated ovarian androgen response in women with PCOS following stimulation by exogenous human chorionic gonadotropin (HCG)²⁸ or by endogenous gonadotropin (after treatment with exogenous gonadotropin-releasing-hormone (GnRH) analogue.^{25, 29} Cultured human theca cells from polycystic ovaries produce 20 times more androstenedione than similar cells from normal ovaries.³⁰ Studies on prenatally androgenized rhesus monkeys and ewes, suggesting that in utero exposure to androgen may permanently diminish hormonal negative feedback on the hypothalamic-pituitary axis, thereby stimulating androgen hypersecretion.

Insulin: Anovulatory women with PCOS are relatively hyperinsulinaemic and more insulin resistant than Ovulatory women with PCOS.^{31, 43} Hyperinsulinemia is probably the result of both increased insulin secretion and decrease in insulin clearance. A study conducted in women with PCOS found to have decreased hepatic insulin extraction.³² Molar ratios of circulating insulin to C-peptide are increased in PCOS, suggesting decreased hepatic extraction of insulin, but such ratios also reflect insulin secretion.³⁵ Causes of the metabolic abnormalities in PCOS remain uncertain, but include an intrinsic abnormality of post-receptor insulin signalling and abnormal insulin secretion.^{31, 33&34} Androgens produce mild insulin resistance. Modest improvements in insulin sensitivity in PCOS during androgen suppression or anti-androgen therapy have been found when less insulin resistant; less obese or non-obese women with PCOS have been studied. However suppressing androgen level does not completely restore insulin sensitivity to normal and administering androgens does not produce insulin-resistance of the same magnitude as that seen in PCOS.^{36, 37} Female rhesus monkeys exposed to androgen excess in utero also exhibit specific impairments of insulin secretion or insulin action depending on whether the androgen excess occurred during early or late gestation respectively.³⁸ Weight reduction in obese women with PCOS significantly improved insulin sensitivity, noting also that the post-diet insulin sensitivity index, after reduction of abdominal adiposity, was normalized compared with weight-matched control subjects. This finding supports the hypothesis that body fat distribution is a major determinant of insulin insensitivity in PCOS. There is a hypothesis that the endocrine environment, especially hyperandrogenaemia, during development (during prenatal life and puberty) has a profound effect on body fat distribution, with a proclivity to abdominal adiposity, thus predisposing to insulin resistance. This hypothesis is supported by data from the study conducted on prenatally androgenized rhesus monkeys that

selectively deposit fat intra-abdominally and exhibit insulin resistance. Other factors which may affect insulin secretion and sensitivity are the age of the female foetus when exposed to androgen excess³⁸. Thus, evidence for abnormal insulin receptor phosphorylation or impaired cell function does not refute the possibility that androgen-dependent body fat distribution is a cause of insulin resistance in PCOS. Many studies suggest that hyperinsulinaemia contributes to the mechanism of anovulation in PCOS women, by interacting with LH to augment steroidogenesis and to induce premature arrest of follicle development.³⁹

LH: If, LH levels are monitored regularly over a period of several weeks, a sudden fall in serum LH concentrations into the normal range can be seen if a spontaneous ovulatory cycle occurs.^{40,41} Nevertheless, LH secretion remains higher than normal (although significantly lower than in anovulatory subjects) in women with polycystic ovaries and regular cycles, but who have symptoms and signs of hyperandrogenism.^{23, 40} This also is a feature of prenatally androgenized rhesus monkeys and ewes, suggesting that in utero exposure to androgen may permanently diminish hormonal negative feedback on the hypothalamic– pituitary axis, thereby stimulating androgen hyper secretion. The mechanism for this LH hyper secretion is not entirely clear, but recent data suggest that in anovulatory PCOS women, the predominant reason for high serum LH concentrations is abnormal negative feedback on LH secretion mediated by either estradiol or progesterone.⁴²

Diagnosis of PCOS: Not all women with PCOS have polycystic ovaries (PCO), nor do all women with ovarian cysts have PCOS. Although a pelvic ultrasound is a major diagnostic tool, it is not the only one. The diagnosis is straightforward using the Rotterdam criteria, even when the syndrome is associated with a wide range of symptoms. The clinical manifestation of PCOS varies from a mild menstrual disorder and signs of hyperandrogenism to severe disturbance of reproductive and metabolic functions. Women with PCOS are predisposed to type 2 diabetes or develop cardiovascular disease. Factors implicated in the low fertility in these patients include anovulation, increased risk of early miscarriage, and late obstetric complications.

Rotterdam European Society for Human Reproduction (ESHRE)/American Society of Reproductive Medicine (ASRM) criteria: In 2003 a consensus workshop sponsored by ESHRE/ASRM in Rotterdam indicated PCOS to be present if any 2 out of 3 criteria are met.⁴⁴

1. Oligo /amenorrhea
2. Clinical and biochemical signs of hyperandrogenism
3. Sonographically confirmed PCOS.

Sonographic features of PCOS include the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume (10 mL). One ovary fulfilling this definition is sufficient to define PCOS.^{58, 59}

National Institute of Health (NIH) criteria: It is recognized that some women with sonographic findings of PCOS may have regular cycles without clinical or biochemical signs

of hyperandrogenism. In such cases Androgen Excess Society (AES) recommended that PCOS should be considered as a disorder of androgen excess and that the NIH diagnostic criteria should be used.⁵⁸In 1990 a consensus workshop sponsored by the NIH suggested that a patient has PCOS if she has all of the following:

1. Oligoovulation
2. Signs of androgen excess (clinical or biochemical)

Future complication of PCOS:

- 1) Cardio vascular disorders⁴⁵
- 2) Diabetes mellitus⁴⁶
- 3) Obesity⁴⁷

- 4) Metabolic syndrome⁴⁸
- 5) Endometrial carcinoma⁴⁹

Diabetes mellitus and IR in PCOS: Most PCOS patients are inherently Insulin Resistant and obese. When assessed overall (obese and lean together), PCOS patients had a 31% rate of impaired glucose tolerance and 7.5% met the criteria for type 2 diabetes mellitus.⁴⁶The prevalence of type 2 diabetes has been reported to be higher among women with PCOS than women without PCOS .For type 2 diabetes mellitus, Metformin is the most widely studied agent thus far and most, but not all uncontrolled studies have shown a significant improvement in insulin sensitivity.⁵⁰⁻⁵³ Troglitazone has similar effects in PCOS patients.^{54, 55} Also, metformin use throughout pregnancy in women with PCOS decreases the rate of gestational diabetes mellitus from ~30% to ~3%⁵⁶. Lifestyle modification reduces the risk of DM to a greater extent (58%).With these results, there may be potential utility in using insulin sensitizers to prevent or delay the onset of type 2 diabetes mellitus in PCOS patients.⁵⁷

Cardiovascular Diseases in PCOS: Many studies have shown that a greater prevalence of diagnosed hypertension or higher ambulatory blood pressure will be there in PCOS patients.⁶⁰⁻⁶³ Women with PCOS may have low HDL-cholesterol, higher levels of LDL-cholesterol, triglycerides homocysteine, plasminogen activator inhibitor type 1; decreased insulin induced vascular relaxation, and endothelial dysfunction.⁶⁴⁻⁷² Some retrospective studies of patients undergoing coronary angiography, found that women with a significant history of hirsutism are more likely to have coronary artery disease. Women with polycystic ovaries on ultrasound are more prone to extensive coronary artery disease than those without such ultrasound findings.^{73, 74} PCOS patients have been shown to have increased carotid intimal media thickness, a 7-fold increased risk of myocardial infarction, and an almost 6-fold increased prevalence of coronary artery calcification versus age-matched control subjects.⁷⁵⁻⁷⁷

Endometrial hyperplasia and endometrial cancer: Oligomenorrhoea or amenorrhoea is known to predispose to endometrial hyperplasia and endometrial cancer in untreated cases. It is good practice to recommend treatment with progestogens to induce a withdrawal bleed at least every 3-4 months.

Metabolic abnormality: Dyslipidemia may be the most common metabolic abnormality in PCOS, although the

type and extent of the abnormalities may vary. Multiple studies have reported similar findings of decreased levels of high-density lipoprotein cholesterol (HDL-C), increased levels of low density lipoprotein cholesterol (LDL-C), and elevated levels of triglyceride in the lipid profiles of PCOS women.^{78, 128, 129}

Obesity: About 50% of women with PCOS are obese. Many studies conducted in different countries revealed that the prevalence of obesity in PCOS varies according to the composition of diet, reduction in activity and geographic location.¹³⁰ Obesity further increases the risk of metabolic and reproductive abnormalities in women with PCOS.¹³¹⁻¹³³

Medical management of PCOS: There is no treatment which reverses the hormonal disturbances of PCOS and treats all clinical features, so medical management is targeted at individual symptoms, and only in association with lifestyle changes.

Allopathic Therapy For PCOS:

Decreasing Testosterone Production and Its action: Excess testosterone production in PCOS is caused by both increased luteinizing hormone stimulation from the pituitary and the effect of hyperinsulinemia at the ovary. Oral contraceptives generally decrease bioavailable testosterone levels by 40% to 60% by decreasing gonadotropin production and increasing sex hormone binding globulin (SHBG).⁷⁹ Weight reduction by improving insulin sensitivity (and thus lowering insulin levels), using both metformin and lifestyle modification, also lowers testosterone to a lesser degree.⁸⁰ Hirsutism score can be improved by the use of metformin (3% to 13%), troglitazone (17%) and second or third generation oral contraceptives (33%).⁸¹⁻⁸⁵

No drug will fully suppress testosterone levels; therefore additional method of blocking testosterone action is useful. Spironolactone (an aldosterone antagonist) has a relative affinity for the testosterone receptor, reduces hirsutism scores (approximately 40%) in about 50% of patients when used alone.⁸⁶⁻⁸⁸

When it is combined with oral contraceptives, the response rate increased to 75% with a reduction in hirsutism scores of about 45%.^{89, 90} The most common side effect is menstrual irregularity, but nausea may also occur.

Management of Infertility: PCOS accounts for 75% of anovulatory infertility. If pregnancies do occur, the miscarriage rate is high in first trimester (30% to 50%).⁹¹ In PCOS, anovulation relates to low FSH concentrations and the arrest of antral follicle growth in the final stages of maturation. Excess LH, androgens, and insulin may individually or collectively play a direct or indirect role in this process, augmenting steroidogenesis but arresting follicular growth. Medications and other options available for the induction of ovulation are reviewed in the following sections.

Clomiphene citrate (CC): CC constitutes one of the first-line treatments for ovulation induction in PCOS patients, as it is economical, has few adverse effects, and requires little monitoring.⁹² CC is an estrogen receptor antagonist that interferes with negative feedback of the estrogen-signalling pathway, resulting in increased availability of

FSH. Increased FSH leads to follicular growth, followed by an LH surge and ovulation. The live birth rate following 6 months of clomiphene ranged from 20% to 40%. Furthermore, the majority of pregnancies occurred within the first six ovulatory cycles following the initiation of treatment.⁹³ CC produces antiestrogenic effects on the endometrium and the cervical mucus.⁹⁵ Obese women with PCOS often do not respond to low doses of clomiphene. Higher doses of clomiphene often may cause side effects and can increase the rate of multiple gestations (around 10%).⁹⁴

Tamoxifen: Tamoxifen is another oral ovulatory agent that is similar to CC in its mechanism of action, but it lacks its antiestrogenic effect on the cervix and endometrium. It can be used as an alternative to CC in case of CC resistance or failure.

Metformin: Metformin is a biguanide currently used as an oral antihyperglycemic agent to manage type 2 diabetes mellitus. The use of metformin is associated with increased menstrual cyclicality, improved ovulation, and a reduction in circulating androgen levels.⁹⁶

Aromatase inhibitors: Selective aromatase inhibitors such as anastrozole and letrozole are new ovulation-inducing agents. They are reversible and highly potent. Letrozole inhibits estrogen production in the hypothalamus-pituitary axis, which implies an increase in gonadotropin-releasing hormone (GnRH) and FSH. It is believed that there exists a relative decrease in aromatase in women with PCOS, which reduces the production of follicles responsible for efficacious ovulation. Aromatase inhibitors selectively block the peripheral passage of androgens to estrogen and thereby reduce the quantity of estrogen and produce positive feedback in the pituitary, leads to an increase in FSH, and optimization of ovulation. The advantage of letrozole is that it avoids peripheral antiestrogenic effects on the endometrium while stimulating monofollicular growth.⁹⁷

Glucocorticoids: Glucocorticoids such as prednisone and dexamethasone have been used to induce ovulation. In PCOS patients with high adrenal androgen, low-dose dexamethasone (0.25–0.5 mg) at bedtime can be used.⁹⁸ Because of their potential adverse effects on insulin sensitivity; its prolonged use should be discouraged.

Gonadotropins: The second possible line of therapy after resistance to CC has been demonstrated in women with PCOS is exogenous gonadotropins.⁹⁹ The mechanism of action of gonadotropins is to induce ovulation, maintain and provoke optimum follicle growth via the controlled administration of FSH, and achieve a follicle capable of being fertilized. Unlike CC, gonadotropin does not exert a peripheral antiestrogenic effect. The main drawback of gonadotropins is that they provoke multiple follicle development, thereby increasing the risk of ovarian hyper stimulation syndrome (OHSS) and multiple pregnancies. Treatment with FSH is expensive, is time consuming, and requires expertise and stringent monitoring. OHSS is related to hCG-mediated production of vasoactive mediators after gonadotropin-induced multifollicular development.¹⁰⁰

Laparoscopic ovarian diathermy: In clomiphene-resistant PCOS women who are unable to comply with the close monitoring necessary for gonadotropin administration, bilateral laparoscopic ovarian surgery with monopolar electrocautery (multiple controlled perforation of the ovary) or laser is an acceptable alternative; both modalities confer similar results.¹⁰¹Laparoscopic ovarian diathermy (LOD) is associated with lower multiple gestation rates than gonadotropins. It appears to be more effective in patients with high LH, and significant reductions in LH and androgens have been shown following surgery. LOD restores menstrual regularity in 63%–85% of women, and the beneficial effects on reproductive outcomes seem to last for several years in many women.¹⁰²

In vitro fertilization techniques: The last possibility for achieving a full-term pregnancy in women with PCOS is to use in vitro fertilization (IVF) techniques.¹⁰³These techniques are used as a last resort when treatments with CC, gonadotropins, and letrozole have failed. IVF is the first choice in cases of concomitant diseases both in women (severe endometriosis, tubal obstruction, etc.) and men (azoospermia, male factor) that reduce the effectiveness of other techniques. IVF with a single embryo transfer significantly reduces the risk of multiple gestations. PCOS does not intervene in embryo implantation therefore the success of IVF techniques is similar to that of patients without PCOS.

Management of androgen-related symptoms: Women with excess androgen may have symptoms like hirsutism, alopecia or acne, which may vary from patient to patient. Oral contraceptive pills (OCPs) reduce hyperandrogenism by promoting direct negative feedback on LH secretion, which results in decreased ovarian synthesis of androgens. OCPs also decrease circulating free androgen, adrenal androgen secretion and inhibit peripheral conversion of testosterone to dihydrotestosterone and promote binding of dihydrotestosterone to androgen receptors.¹⁰⁴ Glucocorticoids suppress adrenal androgen secretion and have been used in patients with adrenal hyperandrogenism. Antiandrogens such as spironolactone, cyproterone acetate (CPA) or flutamide act by competitive inhibition of androgen-binding receptors or by decreasing androgen production.¹⁰⁵ Spironolactone occasionally causes fatigue, postural hypotension, and dizziness, and when administered alone in high doses, it may cause menstrual irregularity and have the risk of feminizing the male foetus, if pregnancy occurs. Gonadotropin-releasing hormone agonist (GnRHa) suppresses pituitary hormones, decreases androgen and estradiol secretion, and improves severe forms of hirsutism. A combination of ethinyl estradiol and CPA is very effective in treating hirsutism and acne. Both OCPs and antiandrogen have been used successfully in the treatment of acne, and alopecia.¹⁰⁶

Natural Remedies for PCOS: A natural drug is likely to be a natural product or compound that is derived from natural sources such as plants, animals or micro-organisms, used for medicinal purpose. Plants became the basis of traditional medicine system throughout the world for thousands of years and continue to provide mankind with new remedies. Compared with synthetic drugs, herbs are

quite safe if used correctly. The world health organization (WHO) estimates that 80% of the population living in the developing countries rely exclusively on traditional medicine for their primary health care needs. In almost all the traditional medicine, the traditional plants play a major role and constitute the backbone of the traditional medicine.

Throughout the human evolution, the importance of natural products for medicine and health has been enormous. Owing to the diverse biological activities and medicinal potentials of natural products, nearly every civilization has accumulated experience and knowledge of their use (Native American, European, Egyptian, Hebrew, Indian, and Chinese).

Herbal drugs:

Liquorice: Liquorice can reduce serum testosterone probably by blocking 17- hydroxysteroid dehydrogenase and lyase. Liquorice can be used as an adjuvant therapy of hirsutism and polycystic ovary syndrome. The herb liquorice is used in natural medicine to treat several conditions including stomach ulcers, infections and osteoarthritis. Additionally, herbal liquorice is used to treat infertility as well as PCOS, and is often combined with other herbs to treat these conditions. Unfortunately, liquorice root can also cause an unwanted interaction with several prescription medications, foods and medical conditions,¹³⁴ so it's a good idea to check with your doctor before using this herb.

Flaxseed: The flax seed is reported to reduce androgen levels with a concomitant reduction in hirsutism reported in thin patients in a case study.¹¹³

Aloe-vera: Aloe vera gel formulation exerts a protective effect against PCOS in Charles Foster female rats by restoring the ovarian steroid status, and altering key steroidogenic activity. This can be attributed to phyto-components present in the extract.¹¹⁴

Cinnamon: Cinnamon extract has been shown to reduce insulin resistance in in vitro and in vivo studies by increasing phosphatidylinositol 3-kinase activity in the insulin signalling pathway in skeletal muscle in rats and thus potentiating insulin action and facilitates weight loss as well.^{115, 119}

Black Cohosh: Black cohosh a herb used to treat symptoms related to hormonal fluctuations that occur in menopause. These symptoms, which include cramping, anxiety and PMS, can also occur if you have PCOS. Do not use black cohosh if you have a pre-existing liver condition or have a hormone-sensitive medical condition.

White peony: It is used in the form of tea, for regulating the levels of the hormone progesterone. Low progesterone levels in women suffering with PCOS, can be successfully remedied if the patient consumes peony tea on a daily basis. Additional benefits of this supplement include the regulation of estrogen and prolactin secretion. These effects observed due to its key ingredients like *Paeoniae radix*, *Paeonia lactiflora*, *Cinnamomi cortex* and *Cinnamomum cassia*.^{116, 117}

Chaste berry: Chaste tree berry, also known as chaste berry, is a herbal remedy used to treat hormonal imbalances in women because it has an immediate effect

on the pituitary gland. This herb is also used to treat symptoms related to PCOS, such as painful breasts, infertility, excess bleeding and excess production of milk. If a PCOS patient is trying to get pregnant or is on a prescription medication for hormonal imbalance, chaste berry should not be used without the expressed recommendation of a physician. The recommended daily dose of chaste berry is 1-4 ml of 1:2 dried plant tincture of 500-1000 mg of dried berries.¹¹⁸

Milk thistle: Milk thistle when used in combination with metformin in treatment of PCOS; patients had produced improved effect on disturbed hormones and ovulation rate.¹²⁰

Saw Palmetto: One of the many symptoms of PCOS is excess hair growth, also known as hirsutism due to overproduction of estrogen hormone. Saw palmetto is a herb that has an anti-androgenic effects that may help to reduce hirsutism. In addition this herbal remedy also facilitates weight loss and increases libido. Saw Palmetto is frequently used together with Vitex Agnus Castus in women with PCOS to help restore hormone balance. It should be taken with a doctor's supervision because it may interact with medications and fertility.²¹

Fenugreek: Fenugreek and Gymnema are typically used in PCOS patients with diabetes and hyperlipidemia. Fenugreek will help to lower cholesterol, fasting glucose levels and postprandial glucose, and improves glucose tolerance. It is a great source of selenium, thiamine, silicon and sodium. Gymnema sylvestre reduces blood glucose, total cholesterol, triglycerides, and LDL and can increase HDL.^{140, 141} Dose: - 1220 mg two to three times daily.

Kasip Fatimah: Reduction in body weight is seen, when ovariectomized rats were treated with Kasip Fatimah herb. This herb produces estrogenic effects and improves insulin sensitivity and lipid profile in PCOS rats without affecting body composition.¹²¹

Chamomile: Chamomile can decrease the signs of PCOS in the ovarian tissue and help LH secretion in rats.¹²²

Spearmint Tea: Spearmint tea had produced reduction in Free and total testosterone levels and degree of hirsutism and increased LH and FSH levels in volunteers in a randomized controlled trial. It was demonstrated and confirmed that spearmint has antiandrogen properties.¹²³

Dandelion Root: Dandelion root contains several minerals and vitamins that are good for the skin. It may alleviate skin conditions such as acne. Dose 540 mg three times a day, preferably with food.

Ginseng saponin: A study done on rats with Poly Cystic Ovary; ginseng saponin found to increase expression of Nerve Growth Factor (NGF) in the ovaries and the brain. Ginseng total Saponin administration attenuated NGF expression in the ovaries.¹²⁴

Tribulus terrestris: Tribulus terrestris has been found to be wonderful in aiding women with menstrual irregularities, improving timing of the entire menstrual cycle. Many herbalists find Tribulus is an effective, overall female fertility tonic and ovarian stimulant, making it an excellent choice for women with PCOS.^{138, 139}

Other Natural Products:

Astragalus polysaccharide: Astragalus polysaccharides plus diene-35 can be effective in improving insulin resistance, high androgen hormone status and lipid metabolism in patients with PCOS and it may be alternative for PCOS.¹²⁵

N-acetyl cysteine (NAC): Prolonged treatment with N-acetylcysteine and L-arginine restores gonadal function in patients with polycystic ovary syndrome. Whether considering NAC as a first line treatment for PCOS, or using it as an adjunct treatment with other medications, research has shown strong efficacy for its use. In some circumstances out performing traditional prescription drugs, and in other cases potentiating the effects of pharmaceuticals. While NAC may not completely reverse PCOS, it shows promise in alleviating many of the chief complaints of PCOS such as hirsutism, infertility, amenorrhea, dysmenorrhea or increased BMI. Combination of CC and NAC significantly increases both ovulation and pregnancy rate in women with CC-resistant PCOS.¹²⁶

Due to the low cost of NAC supplementation, and the high level of efficacy seen, further studies on the use of NAC for PCOS can be beneficial to get a broader scope on when NAC is best used for these patients, in what sort of combination therapies it is the most effective, and among which populations it seems to help most.

D-chiro-inositol: In a study conducted in obese women with PCOS the level of serum free testosterone, plasma triglyceride and blood pressure was found to be decreased and most of them (19 out of 22 women) were ovulated.¹²⁷

Disadvantages of Drugs Used in PCOS: Metformin's most common side effect is stomach upset, usually diarrhoea, but sometimes also vomiting and nausea.

Taking metformin in the middle of a meal may help lessen this side effect. This side effect may also lessen over time, and some women find that particular foods trigger more stomach upset than others.

More serious side effects associated with metformin are liver dysfunction and a rare, but extremely serious side effect, lactic acidosis. While taking metformin the doctor should monitor the patient's kidney and liver functions. People with heart, liver, kidney, or lung disease should not take metformin. The use of metformin to treat infertility related to PCOS is still being researched and different doctors have opposing views on if, when, and how to use metformin to treat infertility.

Clomiphene should not be used for more than six months and, as it is associated with an 11% risk of multiple pregnancies. Women should have ultrasound monitoring during treatment.

Even though second and third generation oral contraceptives have less side effects, on long term use they may cause some of the side effects like Breakthrough bleeding, weight gain, amenorrhea, increased risk of myocardial infarction, increased risk of venous thromboembolism, decreased high-density lipoprotein (HDL), increased low-density lipoprotein (LDL), increased risk of myocardial infarction and increased risk of stroke in smokers and in those with high blood pressure.¹³⁵⁻¹³⁷

Advantages of natural products: Clinical experience and hundreds of medical research studies clearly show that one can get reliable results with natural therapies, especially the foods you eat, the exercise you do and the healing you create with self-selected choices and self-driven behaviour changes that work for you

Modern analytical and structural chemistry have provided the tools to purify various compounds and to determine their structures, which, in turn, has given insights into their action on the human body. Nonetheless, the popularity of natural products will continue simply because they are a matchless source of novel drug leads and inspiration for the synthesis of non-natural molecules¹⁰⁷⁻¹¹¹. In addition, natural products provide important clues for identifying and developing synergistic drugs. If long term medication is needed, then herbs are pretty much safer than conventional drugs. Another advantage is the low cost of herbal products compared to synthetic drugs which are highly priced for the simple reason that researching and testing the products is expensive.

Currently to approve a new synthetic drug, it needs to go through clinical trials with a certain number of selected subjects for several years. The side effects of many of such drugs are undetected until they have been used by a larger population for a longer period of time. Many drugs have been withdrawn from the market after such broader usages because of their high toxicity. However, herbs have been tested by generations and generations of people for thousands of years, and their effects from various aspects have been very well documented, such as those in Chinese medicine. So we actually have more knowledge about herbs than most of the newly approved synthetic drugs.

DISCUSSION

Polycystic ovarian syndrome (PCOS) is a heterogeneous endocrine disorder that affects about one in 15 women worldwide, characterized by elevated levels of male hormones (androgens), insulin resistance, anovulation, infertility, acne and hirsutism. In utero exposure to androgen can lead to excess production of androgen in PCOS women. The age of the female foetus when exposed to androgen excess may affect body fat distribution, insulin secretion and sensitivity. Many studies suggest that hyperinsulinemia contributes to the mechanism of anovulation in PCOS women. Cardio vascular disorders, diabetes mellitus, obesity, metabolic syndrome, endometrial carcinoma are few future complications of PCOS. Metformin gonadotropins, glucocorticoids, aromatase inhibitors, tamoxifen, clomiphene citrate (CC) and second or third generation oral contraceptives are main the allopathic drugs used for the treatment of PCOS. Because allopathic drugs will produce many adverse effects on long term use, herbal products like liquorice, Flaxseed, aloe-vera, cinnamon, black cohosh, white peony, chaste berry, milk thistle, saw palmetto, fenugreek, kasip fatimah, chamomile, spearmint tea, dandelion root, ginseng saponin can be used to treat various symptoms of PCOS with no or mild side effects.

CONCLUSION

In conclusion, it is clear that PCOS is an enigma. Its underlying pathophysiology is not fully understood. No treatment gives complete cure, because treatments, so far, have been directed at the symptoms but not at the syndrome itself. Extensive efforts should be made to fully investigate the syndrome in order to make therapy more successful and to delay the serious long-term effects of the disease on patients' health. Treatment for PCOS will change over time based on what issue is most important to the patient at that stage of her life. PCOS can be treated by use of natural products or allopathic medication. Herbal drugs have promising role in treatment of PCOS and shows steady effect with minimal side effects. They enhance immunity of the body and also regularize menstrual cycle without fluctuating hormonal level. Herbal supplements may take time to cure PCOS but daily usage may treat the disease from its root. In this review, an attempt has been made to study the use of natural remedy for treatment of PCOS.

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