

Polycystic Ovary Syndrome: Current Insights Into Etiology, Symptoms, And Treatment Options

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is an endocrine disorder that is prevalent in women in the reproductive age whereby the ovaries have cysts and are accompanied by symptoms that reduce quality of life. They include the following; Irregular menstrual cycles, Hyperandrogenism characterized by hirsutism, severe acne and some alopecia, Polycystic ovaries are seen on ultrasound examination. The cause of PCOS is not fully understood, but it is concisely known to be multiethnic and multifactorial with insulin resistance being considered as the critical precipitating factor. This insulin resistance sometimes results in high levels of insulin, adding to hyperandrogenism and worsening of the PCOS manifestation. Measures for managing PCOS are diverse; medical and additional or alternative therapies are employed. Most of the allopathic management involve the use of hormonal treatments like the combined oral contraceptives for irregular menstruation and lowering of androgen levels, spironolactone for hirsutism among others, and metformin for insulin resistance. Likewise nutritional intercession is vital in handling of metabolic perversion linked to PCOS. Healthy carbohydrates, which carbohydrates with a less glycemic index, fibre and daily exercise help with weight and metabolic issues. Further, herbal medicine has other potential benefits in the form of complementary therapies: spearmint tea, for example vitex (chaste tree) to name a couple may help to reduce the discomfort and rebalance hormones. PCOS sufferers should be treated individually according to the distinct manifestations because this integrative approach delivers efficient results in managing ailment. Lifestyle changes coupled with pharmacologic and herbal medications enhance the well-being of women with PCOS as well as the reduction of the associated life threatening complications, giving more reason for a better understanding of this illness. Further studies should be conducted to develop new interventions and optimise patient's care, especially patients with PCOS.

Keywords: Hormones, dysfunctional, ovulatory, hyperandrogenism, management, estrogen, anovulation.

1. INTRODUCTION

PCOS is an estrogen-dependent disorder which present with a wide range of phenotypes that include menstrual irregularities, hyperandrogenism, anovulation & polycystic ovarian morphology (PCOM). It is seen in women of child Bearing age and its estimated prevalence ranges from 6 % to 21% depending on the population and the diagnostic criteria adopted (1,2). The long-term risks of combination combined oral contraceptives are better understood and include an elevated risk in PCOS sufferers of type 2 diabetes, cardiovascular disease, and endometrial cancer (3, 4). Also, the procrastinated ovarian cysts are known to be the main causes of an ovulatory infertility, contributing to as much as 80% of women with ovulatory disorders (5, 6).the causes of PCOS are not fully clear. It is accepted as a heterogeneous endocrine disorder accompanied by the enlarged and dysfunctional ovaries, the elevated androgen levels and hormonal resistance to insulin (7). Between one and ten women will develop PCOS in their lifetime prior to menopause, together with relevant comorbidities (8). Even though research established that origins of PCOS include high LH/FSH ratio and heightened GnRH frequency, current studies offer numerous internal and external etiologies: genetic predestination, epigenetics, environment and heredity. However, PCOS is a metabolic disorder also and affects other aspects of life apart from reproduction, including significant cardiovascular diseases, metabolic syndrome, and psychological disorders like anxiety and depression (9-12).The ability to control blood sugar level, reduce inflammation, and improve hormonal balance depends upon practicing several disciplines in parallel,

where the first of these is weight loss. Weight loss by 5% is desirable and sometimes advised in addition to physical activity and changes in the diet that touts low fat/sugar content (13). Pharmacological management of PCOS consists of combined antiandrogen agents, insulin sensitizers oral contraceptives and ovulation inducers; however, all these drugs are currently employed outside FDA approval for the management of PCOS. Research into drug repositioning, where currently approved drugs are used for a different indication has been increasing as well. Potential candidates include; antidiabetic agents, pioglitazone, liraglutide; HMG-CoA reductase inhibitors atorvastatin; Mucolytic agents N-acetyl cysteine (14, 15). Based on the continued rising trends of impacting the health status of women, researchers must continue investigating into the factors contributing to the pathogenesis of the condition and the discovery of other drug targets (16)

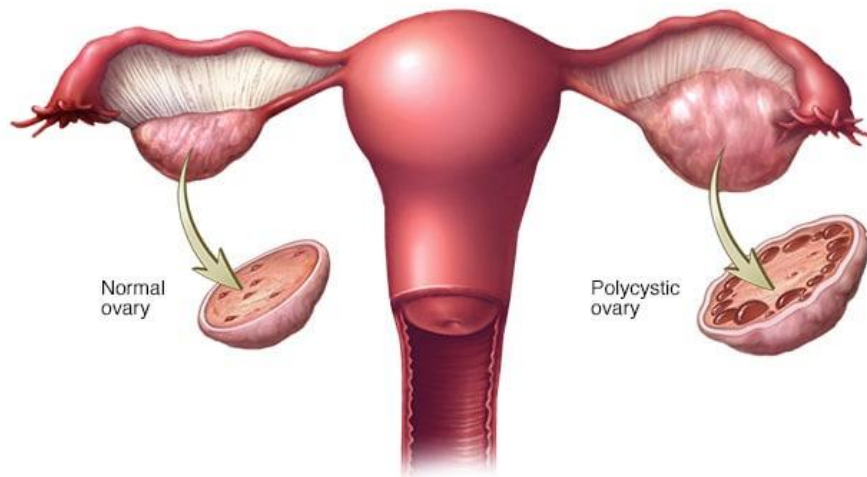


Fig 1: Polycystic Ovary Syndrome (PCOS)

2. SIGNS AND SYMPTOMS

Irregular Menstrual Cycles and Amenorrhea

Women suffering from PCOS have problems with their ovulation, which can manifest in behavioural patterns such as menstrual irregularity other than 35 days or missed periods at all (oligo menorrhoea, amenorrhoea). The irregularity is actually due to disturbances in the cyclical pattern of hormones; androgens are high; follicle-stimulating hormone (FSH) & luteinizing hormone (LH) are imbalanced. This irregularity is attributed to one of the leading causes of infertility in PCOS because the ovary fails to release an egg each month, a condition known as anovulation (17).

Hyperandrogenism (Elevated Male Hormones)

PCOS frequently results to hyperandrogenisms and includes testosterone. This leads into signs such as hirsutism (excessive hairiness on face, chest, and/or back), acne and androgenic alopecia (referring to thinning of hair on the scalp). Androgen excess is a cardinal pathophysiologic feature of PCOS and directly underlies many of the most prominent phenotypes. These symptoms can have prominent psychological effect create body image disturbances, low self-esteem, and mood disorder among women with PCOS (18).

Ovarian Cysts

PCOS is a small, imperfectly developed and fluid-filled sacs in the ovaries called cysts. These cysts can be seen using ultrasound and while common in PCOS, are not needed for diagnosis. These cysts are indicative of hormonal imbalance especially increased levels of LH that forms these cystic follicles. While ovarian cysts are commonly an ovulatory and many patients have no symptoms, some patients experience pelvic or ovarian pain (19).

Insulin resistance and Obesity

About eight out of ten women with PCOS suffer from insulin resistance, in which their body tissues are unresponsive to the hormone insulin. This results in compensatory hyperinsulinemia where the body in effect increases on the production of the hormone. This dysregulation insulin can cause fat increases storage in the abdominal cavity resulting in weight gain and obesity. PCOS patients with insulin resistance are likely to develop metabolic syndrome, type 2 diabetes, and cardiovascular disease (20).

Infertility

Limited or absent ovulation, getting pregnant is very hard for women with PCOS. This disruption of the hormonal cycle inhibits the development and release of an egg in the woman's reproductive cycle each month sufficiently to allow for

fertilization. Such can prolong endeavours to get pregnant, and may prove to be very upsetting especially to women who are longing to have a child. It also should be mentioned that PCOS is one of the leading reasons for infertility in women (21).

Mood Disorders and Depression

Women with PCOS are more likely to suffer from either depression or anxiety. They are mainly connected with the physical and psychological load of the PCOS manifestations included overweight/obesity, acne, and infertility, and hormonal changes. Psychiatric disorders in PCOS have a deleterious impact on health-related quality of life and may need both pharmacological and psychological intervention (22).

Sleep Apnea

OSA is more prevalent in women who are PCOS sufferers and, most significantly, those who are overweight. It is a condition that leads to temporarily stops in breathing during sleep and poor sleep quality meaning the patient feels sleepy during the day. Sleep apnea is also related to some diseases such as cardiovascular disease, insulin resistance and depression (23).

Acanthosis Nigricans- skin changes

Description: Acanthosis nigricans is a skin disorder that manifests itself in the form of dark and velvety skin lesions involving the neck, axillae or groins. There is often associated with insulin resistance.

Impact: These skin changes act as positive markers for insulin resistance in PCOS and might trigger further assessment and intervention of other metabolic abnormalities (24).

3. CAUSES

Polycystic Ovary Syndrome (PCOS) is a chronic endocrine disorder in women of reproductive years. The exact cause of PCOS has not been determined, but studies show that most PCOS is caused by genetic, hormonal and environmental factors. Here are some of the major causes associated with PCOS:

1. Insulin Resistance:

Hypersensitiveness to insulin is now well known as one of the major causes associated with PCOS. Women with insulin resistance experience what precisely: the body's cells change their reaction to insulin, a hormone that controls blood sugar levels. This results to increased release of insulin by the pancreas hence hyperinsulinemia can result. Elevated insulin levels stimulate androgen (male sex hormones like testosterone) production and lead to PCOS like symptoms, including missed periods, excessive hair, and skin breakouts.

2. Hormonal Imbalances:

PCOS is characterized by increased androgen concentrations that affect ovary and menstruation in women. Hyperandrogenism is a characteristic feature of PCOS and plays a role for many clinical manifestations of the disease including hirsutism, acne, and female androgenetic alopecia.

3. Genetic Factors

The studies reveal some evidence pointing to the fact that PCOS is hereditary, meaning that it may be embedded in genes. Daughters of women with PCOS or women suffering from the disease themselves are at a high risk. For instance, there are genetic factors related to impaired insulin signalling, androgen signalling disturbances in PCOS (25, 26).

4. Low-Grade Inflammation

One of the most significant issues that women with PCOS are struggling with is a high level of inflammation. This inflammation is believed to cause polycystic ovaries to secrete androgens which lead to insulin resistance and cardiovascular diseases.

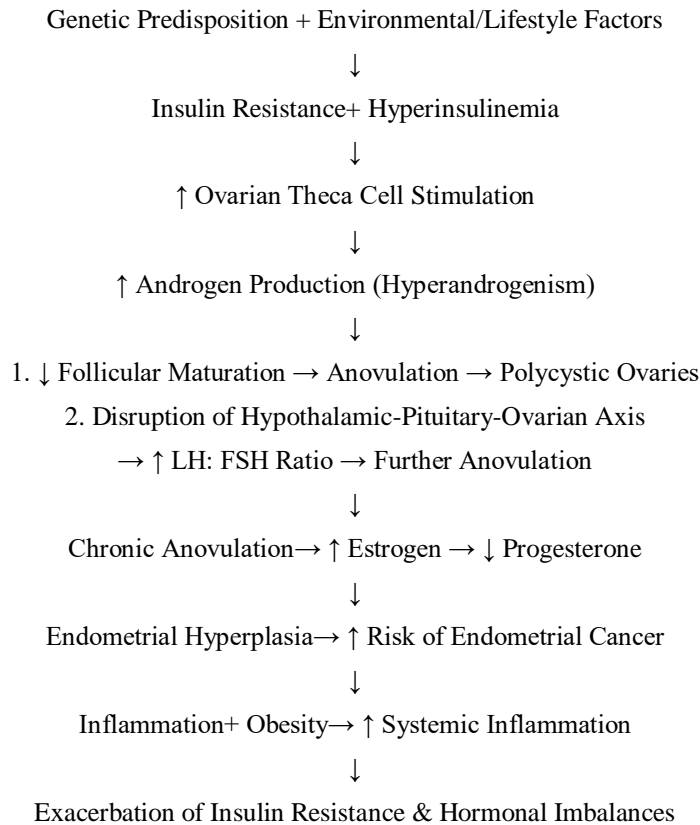
5. Obesity

There is no evidence that directly links obesity to PCOS, but the disorder can worsen due to increased insulin resistance brought by obesity. On the other hand, not all the women with PCOS are overweight, this implies that weight has a small role to play on this disease (27, 28).

6. Environmental and Lifestyle Factors

Diet, stress and lack of exercise may have the potential to cause the development of PCOS. Another factor postulated to be responsible for dysregulation of hormones is exposure to endocrine-disrupting chemicals (EDCs) within environment; the relationship between EDCs and hormonal dysregulation was also put forward, yet the possibility remains under discussion (29).

4. PATHOPHYSIOLOGY (30, 31)



5. MANAGEMENT OF PCOS

Polycystic ovary syndrome cannot be completely treated; the treatment that is used in clinical practice is only for relieving the symptoms that are associated with PCOS. Most of the Hormonal imbalances that are associated with PCOS are not reversed; relief in symptoms is essentially due to lifestyle changes. Till now, efforts have been towards treating anovulation, infertility, or symptom management related to PCOS. Till now, treatments for PCOS are

1. Allopathic therapy
2. Herbal therapy
3. Lifestyle and diet changes

6. ALLOPATHIC THERAPY (32-38)

1. Clomiphene Citrate (CC)

Clomiphene citrate belongs to the class of SERM and is used as the first-line for ovulation induction in PCOS for almost five decades now. It competitively inhibits the estrogen receptors in hypothalamus, raises GnRH pulse frequency and thus enhances the release of FSH and LH. CC is normally taken at 50 mg per day and then titrated up to 150 mg per day over five days. It has a pregnancy success rate of approximately 30% but 20 percent of those pregnancies are at risk for miscarriage or stillbirth. Some of the side effects are OHSS; multiple Births, Hot flashes, fatigue and others are a combination of the two.

2. Aromatase Inhibitors (Letrozole)

Letrozole is one of the third generation Selective aromatase inhibitors, which is utilized in the treatment of ovulation induction in the PCOS women. It does so by lowering estradiol levels that make the follicular layer highly responsive to FSH thereby raising ovulation frequency. Letrozole has the effect of aromatization inhibitors and competes for enzymes that aromatize androgens to estrogen, hence raising levels of GnRH and FSH, which stimulates ovulation.

3. Gonadotropins

Gonadotropins are employed in second-line treatments with women who do not manage first-line drugs such as Clomiphene citrate and Letrozole. These exogenous hormones encourage growth and maturation of Ovarian Follicle but come with complications such as multiple pregnancies as well as Ovarian Hyper stimulation Syndrome.

4. Insulin Sensitizing Agents

Abnormality in insulin signalling is a primary factor in the development of PCOS. Hypersensitization of insulin for a long time results in hyperandrogenism and disarray in the development of follicles. The anti-diabetic drug used in the treatment of insulin resistance in PCOS include drugs such as metformin. Additional details about one oral agent is metformin, which enhances insulin mediated glucose utilization and decreases hepatic glucose output. The recommended dose for initial week is between 500 mg and 850 mg per day with gradual titration up to 2000 mg per day if well endured. This produce side effects such as gastrointestinal upset and vitamin B12 deficiency.

5. Inositol

Inositol is a nutritional supplement which has been suggested to enhance insulin sensitivity and ovarian action, however, there is only a bit of evidence proving its effectiveness. Highly recommended as a low-risk treatment option that relatively cheap and produces few side effects.

6. Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RA)

Liraglutide classified as GLP-1 receptor agonists, enhances the strength of insulin response and the action of insulin receptors. They suggested that these drugs hold a promise in treating metabolic symptoms of PCOS due to effectiveness in weight management and glycemic control.

7. Statins

Atorvastatin has been prescribed to control the dyslipidemia that is characteristic of PCOS and is a strong predictor of CVD. They are reported to lower the level of LDL cholesterol, triglycerides and turn down oxidative stress parameters. However, since they may cause birth abnormalities, they are discouraged for use by women of childbearing age.

8. Antiandrogens

Cyproterone acetate, spironolactone, flutamide and finasteride are sometimes used to control hirsutism, acne and seborrhoea by minimizing the effect of androgens. Spironolactone is used most often because it is the safest and the cheapest drug among all medications of this group. But these medications should be prescribed with contraception because of the possibility of teratogenic effects.

9. Oral Contraceptives (OCs)

OCs should be initial choice therapy for menstrual irregularities, hirsutism and acne in women with PCOS. They operate through inhibition of gonadotropins, and decrease in ovarian androgen synthesis, and hormonal control of the menstrual cycle. Estrogen and progestogen combined oral contraceptives should be used while choosing the contraceptive agents. Nevertheless, attention should be paid to tendencies towards thromboembolic episodes and hypertension, especially in overweight or smoking women.





10. Medroxy progesterone acetate (MPA)






MPA may be prescribed to woman with PCOS with irregular cycles not seeking conception to help rectify a condition of amenorrhea or uncontrolled uterine bleeding through the suppression of ovarian androgens. Those endocrine functions consist of enhancing the sensitivity to insulin, as well as the lipid metabolism profile.






11. in Vitro Fertilization (IVF)




Infertility patients who do not get pregnant when using ovulation induction therapies have the option of using IVF. Women with PCOS have comparable IVF success rates with those without PCOS when single embryo transfer is applied in order to avoid multiple gestations

7. HERBAL THERAPY

Sl,no	Herb name	Image	Herb used	Chemical constituent
1.	<i>Cinnamomum zeylanicum</i> Cinnamon		Bark	(E)-Cinnamaldehyde
2.	<i>Gymnema sylvestre</i>		leaves	Betaine, Gymnemic acid, tartaric acid, gurmarin, calcium oxalate, glucose, choline, stigma sterol
3.	<i>Mentha spicata</i>		leaves	Carvone, limonene and 1,8-cineole
4.	<i>Pergularia daemia</i>		leaf	Glycosides, Alkaloids, steroids, flavonoids, saponin, tannin, phenolic compounds, terpenoids, carbohydrates, gums and mucilage.

5.	<i>Saraka indica</i>		Bark	Tannins, flavonoids, phytosterols, alkanes, esters, anthocyanin pigments, fatty acids and carbohydrates.
6.	<i>Serenoa repens</i> (Saw Palmetto)		Fruit	Free fatty acids (85%) or esterified fatty acids (approximately 2% methyl-ethyl esters triglycerides).
7.	<i>Tribulus terrestris</i>		Fruit and Root	saponins, alkaloids
8.	Withania somnifera		Root	Alkaloids, Saponins, Flavonoids, Iron and other trace elements
9.	<i>Glycyrrhiza glabra</i>		Root	Glycyrrhizin, Flavonoids, Phytoestrogens, Polysaccharides, Coumarins

10.	<i>Aloe Vera</i>		leaves	Aloin, Amino Acids , Polysaccharides, Saponins , Phytosterols, Gibberellins and auxins
11.	<i>Linum usitatissimum</i>		Seeds	Lignans , Alpha-Linolenic Acid (ALA), Fiber, Protein and Amino Acids, Vitamins and Minerals
12.	Curcuma longa		Rhizome	Curcumin , Demethoxycurcumin, Bisdemethoxycurcumin, turmerone, atlantone, zingiberene, Polysaccharides
13.	<i>Actaea racemosa</i>		Rhizome and Root	Actein, Cimicifugoside, 27-Deoxyactein, Isoflavones, Phenolic Acids, Tannins, Resins, Alkaloids and Flavonoids
14.	<i>Paeonia lactiflora</i>		Root	Paeoniflorin, Albiflorin, Tannins, Flavonoids , Polysaccharides

15.	<i>Chaste Tree Berry</i>		Fruit	Iridoid, Glycosides, Flavonoids Diterpenes, cineol, limonene, and sabinene
16.	<i>Urtica Dioica</i>		Root and Leaf	Quercetin, kaempferol, caffeic acid and chlorogenic acid, Lignans, Sterols, Polysaccharides, Minerals
17.	<i>Camellia sinensis</i>		leaves	Catechins, tannins and flavonoids, Caffeine , Theanine, Vitamins and Minerals

1. *Cinnamomum zeylanicum* Cinnamon

Cinnamon has been significantly proved to control metabolic as well as reproductive symptoms in women with PCOS. Its anti-androgenic effects are thought to arise from lowering insulin and insulin like growth factor-1 (IGF-1), which is alleged to inhibit the synthesis of testosterone in the ovaries. Cinnamon also reduces insulin resistance through PI-3 kinase, increases glucose metabolism and raises the levels of GLUT -4 which helps to transport glucose across the cell membrane. It also helps in regulating menstrual cycles and has hypolipidemic effect by decrease absorption of cholesterol and increase expression of PPAR α (39, 40).

2. *Gymnema sylvestre* (41)

Conventional medicine in the treatment of diabetes, *Gymnema sylvestre* has shown to improve the condition of women with PCOS by reducing their serum androgens and therefore improving their insulin sensitivity. It also facilitate in regulation of menstrual cycle by promoting the insulin sensitivity and altered glucose metabolism pathways.

3. *Mentha spicata* (Spearmint) (42)

Spearmint has been established to be effective in CEOs both in metabolic and reproductive systems disorders in PCOS. As an anti-androgen, it has been used to help decrease testosterone, and has helped clients with hirsutism and/or irregular menses.

4. *Pergularia daemia*

This plant is thought to have a role in normalizing hormonal levels in patients with PCOS – by regulating testosterone and the luteinizing hormone and decreasing progesterone and the follicle stimulating hormone in experimental animal models of PCOS. In particular it has also been productive in solving menstrual problems and also in the elimination of ovarian cysts (43).

5. *Saraka indica*

Commonly called by its Hindi name Ashwagandha, used in Ayurvedic and Unani treatments for women reproductive tracts,

Saraka indica has been found to stimulate the uterine and endometrial tissue, and assist in conditions like menorrhagia and amenorrhea. This it may help to regulate hormonal balance in women with polycystic ovary syndrome due to its uterotonic form (44).

6. *Serenoa repens* (Saw Palmetto)

Saw palmetto helps control hormonal fluctuations and combat conditions like hirsutism and acne common to women with PCOS. It also provides reproductive health to both male and female (45).

7. *Tribulus terrestris*

Popular for enhancing fertility and preventing return of ovarian cysts, *Tribulus terrestris* enhances hormonal balance and possess anti-estrogenic properties that helps to release gonadotropin. It has other benefits in management of PCOS including hypoglycemic and lipid profiles (46).

8. *Withania somnifera* (Ashwagandha)

Withania somnifera commonly known as Ashwagandha lowers stress, a factor that has been found to disrupt ovarian function and reproductive hormones resulting in PCOS. This is also good for the endocrine system and might likely help with menstrual regulation too (47).

9. *Glycyrrhiza glabra* (Licorice)

Another research reveals that liquorice has the potential in the decrease the testosterone level and manage hirsutism and other signs. Typically, it is applied as a complementary therapy to endocrine therapy in patients with PCOS (48).

10. *Aloe Vera*

Aloe Vera has demonstrated efficacy of modulating ovarian steroid concentrations besides reversing impaired ovarian structure in PCOS in animals. It might work through correcting steroidogenic action and controlling the degree of cyclicity of oestrous cycle (49).

11. *Linum usitatissimum* or Flaxseed

Flaxseed which contain lignans suppress androgen levels and resolve hirsutism. Supplementation has been found to enhance the condition in women with PCOS affecting hyperandrogenism and metabolic dysfunction (50).

12. *Curcuma longa* (Turmeric)

A study revealed that curcumin, the bioactive existing in turmeric, exerted the efficacy of clomiphene with regard to decreasing androgen levels and enhancing ovulation in rats with PCOS (51).

13. *Actaea racemosa* (Black Cohosh)

Often prescribed for symptoms caused by hormonal imbalances, Black Cohosh might help in relieving menstrual pain and restore hormonal balance. It proves effective in controlling mood swings, anxiety, and other hormonal fluctuations experienced in the PCOS patient; but there are side-effects, like vomiting and diarrhoea (52)

14. *Paeonia lactiflora*: White Peony

It is widely used to help to bring a balance to Progesterone and Luteinizing Hormone (LH). Daily use may reduce estrogen and prolactin concentrations which assist the menstrual cycle in PCOS (53).

15. Chaste Tree Berry (*Vitex agnus-castus*)

Popular for regulating the pituitary gland, Chaste Berry can effectively work in order to alleviate some of the symptoms such as anovulation, amenorrhea and pelvic. However, it should be used with a lot of care by pregnant women or people on the use of birth control measures (54).

16. *Urtica Dioica*

It is also known as Stinging Nettle, Stinging Nettle also raises SHBG, making testosterone levels less free, and rebalancing hormones. It is also prescribed for managing hyperandrogenism linked with PCOS, but this treatment results in hypotension when used in the long-term (55).

17. *Camellia sinensis* (Green Tea)

Green tea has an impact on body weight and insulin sensitivity in women with PCOS. It has also proved effective in normalizing levels of gonadotropin and in prevention of the formation of ovarian cysts, which is useful in treatment of PCOS (56).

8. LIFESTYLE AND DIETARY MODIFICATIONS

1. Fat Intake: According to WHO recommendation, total fats should not exceed 30% of total energy with saturated fats not more than 10%. A variety of research has suggested that replacing saturated fats, for instance with unsaturated fats found in cooking oils or spreads, has glucose-insulin improving effects in normal and diabetic people. Data suggest that PUFAs from fish oil may improve insulin levels and metabolism in general, but there is not much information on PCOS (57-59) Reduction of trans fats should be made because of the link with infertility rate (60,61).

2. Protein Intake: Since protein affects glucose and insulin homeostasis, and contributes to control of hunger, higher protein diets may help in weight loss. However, it is also important to control proteins with experts recommending that protein should not exceed 20 % of the total energy requirement. High protein can enhance the glycemic control and will be useful in maintaining muscle tissue during exercising (62,63)

3. Carbohydrate Management: Low glycemic index diets enhance insulin response and decrease triglyceride levels and increase HDL cholesterol. Although also low-GI, whole grains may also assist in reducing diabetes risk. This short-term low carbohydrate diet appears effective with weight loss and a variety of other cardio metabolic outcomes, but altered lipid profile may become problematic in the long term (64, 67).

4. Dietary Supplements: Myo-inositol, as a supplement which has been known to help regulate insulin and reproductive hormones, has been helpful to bring normal ovulation cycle in a PCOS patient. Perhaps, greater improvements would occur if a low glycemic diet and exercise were taken concurrently (68, 69).

5. Mediterranean Diet: While few investigations on the Mediterranean diet of high MUFA from olive oil source has shown positive effects in obesity and insulin resistance both of which are major focuses when it comes to management of PCOS (70).

6. Meal Patterns: The timing of meals is crucial; when people eat at irregular intervals, or do not eat breakfast, it reduces insulin sensitivity index and increases fat gain. A structured eating pattern is beneficial to improved metabolic health in both lean and obese women (71).

9. CONCLUSION

Polycystic Ovary Syndrome (PCOS) is essentially a multiple-system disorder which affects women of the reproductive age psychologically and physically. Due to diverse manifestation, including, but not limited to hormonal dysfunction, insulin resistance, psychological discomfort, and even infertility, it is crucial to employ an individualised and multidisciplinary approach to the treatment of PCOS. Pharmacological therapies, natural remedies and an adjustment of life patterns suggest several ways to allow symptom relief and thus enhance the client's quality of life. Nonetheless, more investigations are needed to locate the root of PCOS and to deploy accurate therapies for the illness. Working with clients to design programs consistent with recent research about PCOS and healthy lifestyle changes combined medical treatments with complementary treatments; healthcare practitioners may promote better PCOS self-management and improved quality of life for women with this condition.

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