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Polycystic Ovary Syndrome: An In-Depth Examination of Pathophysiology, Causes, Symptoms, and Natural Treatments

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Abstract

Polycystic Ovary Syndrome (PCOS) ranks among the most prevalent endocrine disorders affecting women of reproductive age, characterized by a variety of phenotypes including metabolic, reproductive, and endocrine irregularities. The causes of PCOS are multifaceted, incorporating genetic factors, environmental influences, and internal mechanisms such as insulin resistance, hyperandrogenism, and chronic inflammation. Symptoms of PCOS include irregular menstrual cycles, hirsutism, acne, obesity, and infertility, with long-term complications that may involve diabetes and endometrial disorders. Traditional treatment approaches focus on lifestyle changes, weight control, and pharmacological therapies; whereas natural remedies like spearmint, ginseng, chaste berry, chamomile, shatavari, coconut, and flaxseeds demonstrate potential in hormone regulation, ovulation enhancement, and symptom relief. A comprehensive understanding of the underlying pathophysiology is crucial for the formulation of effective and holistic management strategies.

Keywords: Polycystic Ovary Syndrome, Hyperandrogenism, Insulin Resistance, Inflammation, Natural Remedies, Hormonal Imbalance, Reproductive Health

Introduction

Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder affecting women. It can present itself in various phenotypes, which may include metabolic, endocrine, and reproductive alterations, along with numerous potential combinations of symptoms. PCOS is defined by anovulation and dysfunction within the hypothalamic-pituitary-ovarian axis. In contrast to other causes of ovulatory failure, which may involve either suppressed gonadotropin secretion or inadequate ovarian follicle development, or a combination of both, PCOS typically features androgen excess and subtle variations in serum levels of gonadotropins and estrogens that are often undetected by standard testing. The serious consequences of PCOS can include an increased risk of endometrial hyperplasia and neoplasia ^[1]. Additionally, insulin resistance (IR), metabolic syndrome (MS), and low-grade chronic inflammation are examples of non-reproductive manifestations associated with PCOS ^[2-6].

Approximately half of those diagnosed with PCOS are classified as overweight. Therefore, it is essential to adopt a weight loss strategy alongside a healthy, balanced diet and regular physical activity, which can enhance metabolic rates, improve insulin sensitivity, and facilitate weight loss ^[7]. Recent advancements in understanding the pathophysiological mechanisms of PCOS have been significant (Figure 1), resulting in enhancements in both diagnosis and treatment options. We will discuss a few of these advancements based on our evaluation of those that have had the most substantial impact on the management of women affected by this syndrome.

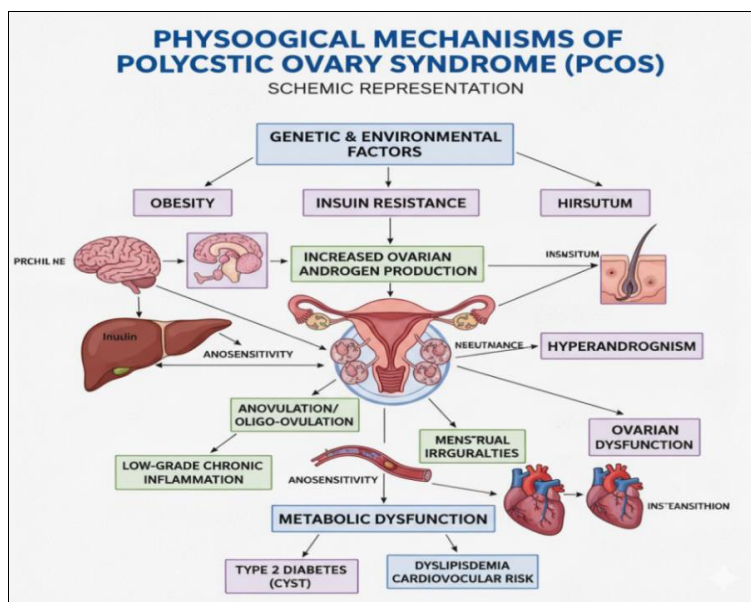


Fig 1: A Diagrammatic Illustration Of Various Pathophysiological Mechanisms Associated With Polycystic Ovary Syndrome.

Factors Contributing To PCOS

There are numerous external, environmental, and internal factors that contribute to the onset of PCOS.

1. External factors

Genetic mechanisms: The types of genes associated with the development of PCOS can be classified as follows: genes that play a role in the steroidogenesis of the ovaries and adrenal glands, genes that are involved in the regulation and action of steroid hormones, genes that influence insulin action and secretion, genes that affect energy homeostasis, and genes that are associated with persistent inflammation [8]. Consequently, the emergence of PCOS is attributed to specific alterations in certain genomes. Some of the genes implicated in the development of PCOS include Calpain 10 (CAPN10), cytochrome P450, insulin, androgen receptor (AR), fat mass obesity (FTO), and follicle-stimulating hormone receptor (FSHR) [9].

2. Environmental factors

PCOS may also arise due to exposure to endocrine-disrupting chemicals (EDCs). The Endocrine Society defines endocrine-disrupting chemicals as "an exogenous chemical, or a mixture of chemicals, that interfere with hormone action." These substances can adversely affect the endocrine system^[10]. Commonly encountered EDCs include Bisphenol A (BPA), perchlorate, dioxins, phthalates, phytoestrogens, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), triclosan, perfluoroalkyl and polyfluoroalkyl substances (PFAS), and pesticides such as dichlorodiphenyltrichloroethane (DDT) and its metabolite (DDE), along with organophosphorus compounds, alkyl phenols (surfactants), parabens, methoxychlor, diethylstilbestrol (DES), the fungicide vinclozolin, and natural hormones^[10-11]. EDCs can act as either agonists or antagonists by binding to hormone receptors, which can lead to an increase, decrease, or cessation of hormone activity^[12].

Women may experience elevated levels of inflammatory mediators, which can disrupt normal steroidogenesis, particularly if they are exposed to air pollutants such as particulate matter (PM) 2.5, sulfur dioxide, nitrogen oxides,

and polycyclic aromatic hydrocarbons (PAHs), thereby contributing to the development of PCOS [13].

Diet: A diet high in fats, particularly saturated fatty acids, along with the consumption of foods that have a high glycaemic index, elevates the risk of insulin resistance and its associated complications, such as obesity and PCOS [14].

1. Internal factors

- **Insulin resistance:** Insulin resistance and the resulting compensatory hyperinsulinemia are prevalent characteristics of PCOS. Research indicates that hyperinsulinemia enhances ovarian androgen production and disrupts ovulation, contributing to the hyperandrogenism associated with the disorder. This occurs due to insulin stimulating theca cells, which are ovarian cells responsible for producing testosterone through androgen biosynthesis ^[15].
- **Hyperandrogenism:** This condition arises from the excessive production of androgens due to dysfunctional ovarian activity and insulin resistance. Hyperandrogenism impedes the development of follicles, the ovarian sacs where eggs mature, and obstructs normal ovulation ^[16].
- **Inflammation:** The etiology of PCOS may be affected by cytokine gene polymorphisms and the imbalance between pro-inflammatory and anti-inflammatory cytokines. Consequently, the development and worsening of the metabolic features of PCOS are influenced by inflammatory responses. Adipocytes can increase the production of substances that promote inflammation, potentially leading to chronic inflammation ^[17]. Inflammation directly stimulates the ovaries to overproduce androgens. The extent of abdominal adiposity, which contributes to the inflammatory burden in PCOS, may be affected by hyperandrogenism ^[18]. Studies have associated elevated androgen levels with inflammation.
- **Obesity:** Obesity activates theca cells that stimulate luteinizing hormones, resulting in an excess of ovarian androgens. Elevated androgen levels can lead to irregular menstrual cycles and obesity ^[19].

Symptoms of PCOS

The majority of women are unaware that they have PCOD. It is crucial to recognize these signs in order to detect the issue at an early stage. Symptoms of PCOS can commence shortly after puberty, but they may also appear in early adulthood.

It presents numerous signs and symptoms:

1. **Irregular periods:** This is the most common symptom of PCOD. The condition typically first presents as irregular or concerning menstrual cycles. It is important to monitor your monthly cycle closely to identify PCOD [20-21].
2. **Excessive facial and body hair:** The term hirsutism refers to excessive growth of facial hair. Women with PCOD experience increased hair growth due to their ovaries producing elevated levels of the male hormone androgens [20-21]. Hirsutism is a prevalent clinical sign of PCOS, affecting up to 70% of women with hyperandrogenism. Areas that may be affected by excessive hair growth include the face, arms, back, chest, thumbs, toes, and abdomen, all of which are linked to hormonal fluctuations associated with PCOS [20].
3. **Mood Swings:** PCOD leads to irregular periods and hormonal imbalances. This hormonal disruption can result in sudden mood swings, with common symptoms including anxiety and depression [22].

Pelvic Pain: In addition to severe bleeding and headaches, pelvic pain may occur during menstruation [20].

1. **Skin Darkening:** Dark patches may develop on various areas of the body, including the neck, groin, and beneath the breasts [22].
2. **Weight gain:** Women with PCOD often experience rapid weight gain due to their bodies producing high levels of male hormones and insulin. An excess of fat in the lower abdomen is a common indicator of PCOD [20]. There are notable national variations in the prevalence of overweight and obese women within PCOS communities. In Kuwait, 37% of women with PCOS are classified as overweight but not obese, in contrast to 10% in Italy. Research conducted in the US and Australia indicates that women with PCOS have the highest obesity rates, with 61% to 76% of them being classified as obese [21].

8. Acne and Oily Skin: Hormonal imbalances associated with PCOD result in acne and various facial issues. An overproduction of male hormones is responsible for the occurrence of acne. Some women suffering from PCOD may experience severe cystic acne [22]. Acne is classified as an inflammatory condition that impacts the sebaceous and apocrine glands linked to hair follicles. For women dealing with acne, excessive sebum production is the primary concern, while serum androgen levels are often not elevated [23].

9. Diabetes: Women with PCOD exhibit elevated insulin levels, which increases their susceptibility to diabetes [20]. Insulin resistance is one of the hallmark features of PCOS. Epidemiological research has provided substantial evidence connecting PCOS with an increased risk of type 2 diabetes, impaired glucose tolerance (IGT), and gestational diabetes mellitus (GDM). There exists a relationship between PCOS and GDM. Although research on prevalence has been

limited thus far, a recent meta-analysis indicates that women with PCOS are generally three times more likely to develop this condition [21].

Pathophysiology

Excess levels of androgen and insulin resistance are merely two of the numerous pathological features that characterize PCOS, a complex underlying condition [24].

1. Impact of Elevated Androgens

The maturation of follicles is crucial for normal ovulation. However, this process is hindered by elevated levels of androgens [25]. Excessive androgen production obstructs ovulation by preventing multiple follicles from developing into a single dominant follicle. Furthermore, since androgens are converted into oestrogen in peripheral adipose tissue, particularly in individuals with obesity, they contribute to increased estrone levels. This sustained rise in estrone levels disrupts menstrual regularity by inhibiting oestradiol, a hormone essential for initiating the LH surge during ovulation. Consequently, disrupted LH surges can lead to anovulation and potential infertility, as they interfere with the timely occurrence of ovulation and follicular development [26]. The growth of follicles is adversely affected by consistently high estrone levels and imbalanced LH, resulting in anovulation. The failure of small preantral follicles to mature into dominant follicles leads to degeneration, which may affect the ovarian stroma, increase ovarian volume, and result in a large, polycystic-appearing ovary [27].

2. Impact Of Anovulation on Health

Ovulation typically occurs between days 1 and 14 of the menstrual cycle. When ovulation does not occur properly and follicles continue to develop, the availability of progesterone is diminished, and the formation of the corpus luteum is affected due to elevated levels of estrone altering the conversion of dominant follicles. To maintain the stability of the endometrium, progesterone is essential. The endometrium is expected to proliferate and thicken in response to the release of estrogen during the initial phase of the menstrual cycle. This preparation is crucial for the implantation of a fertilized egg. If implantation does not take place, the corpus luteum, which produces progesterone, will degenerate. Patients experiencing excessive menstrual bleeding may have a history of irregular cycles. This pattern of irregular and heavy bleeding is characteristic of anovulatory bleeding, which occurs when the ovaries fail to release an egg each month. This condition can arise from various factors, including hormonal imbalances, polycystic ovary syndrome (PCOS), amenorrhea, and oligomenorrhea.

3. Hormonal Changes Observed In PCOS

In patients with PCOS, serum levels of testosterone, DHEA, and androstenedione increase due to heightened hormone production. There is also a significant rise in LH levels, which facilitates the ovaries' production of testosterone. In individuals with PCOS, the LH:FSH ratio typically exceeds 2:1, while in healthy individuals, it remains below 1:1. Lower levels of the testosterone-binding hormone SHBG result in elevated testosterone levels, thereby increasing the risk of hyperandrogenism, hirsutism, and hair loss. Additionally, women with PCOS exhibit higher total estrogen levels, but the ratio of estrone to estradiol is

reversed. In these women, estrone is the dominant form of estrogen, whereas estradiol is normally predominant.

Natural remedies in management of PCOS:

1. **Spearmint:** The aromatic, rhizomatous perennial herb known as spearmint (*Mentha Spicata*) belongs to the Lemnaceae family. This plant family is rich in polyphenols, which contribute to its strong antioxidant properties. A 30-day randomized controlled trial investigated the effectiveness of spearmint tea in reducing hirsutism among women with PCOS. Additionally, studies conducted on rats with PCOS indicated that spearmint oil from *Mentha spicata* enhanced the number of graafian follicles while simultaneously decreasing body weight, testosterone levels, ovarian cysts, and atretic follicles [28-29].
2. **Ginseng:** The scientific designation for ginseng, which is part of the Araliaceae family and the genus *Panax*, is *Panax ginseng*. This enduring medicinal plant is characterized by its potent aroma. It is recognized for its significant antioxidant properties. The antioxidant enzymes glutathione and superoxide dismutase are activated, enhancing these antioxidant effects. By mitigating the activity of hydroxyl radicals and anions, antioxidants facilitate the removal of superoxide and prevent lipoidal peroxidation in cellular membranes. This action can lead to a notable reduction in plasma LH levels and an improvement in the endocrine profile of PCOS patients experiencing ovulation issues [30].
3. **Chaste berry:** The chaste berry, scientifically known as *Vitex agnus-castes*, is also a member of the Lemnaceae family. It is widely recognized for its ability to address hormonal imbalances and enhance fertility. The berry contains compounds such as astacin, astacin acetate, astacin glucoside, *Agnus ide*, *Agnus ide* glucoside, and vitexin. It promotes an increase in progesterone levels while decreasing testosterone levels, without affecting DHEA or oestradiol levels. Furthermore, it stimulates and stabilizes the activity of the pituitary gland, which is responsible for the release of luteinizing hormone, thereby reducing estrogen and androgen levels through the elevation of progesterone levels. Consequently, it is the most commonly utilized treatment for PCOS [31,32].
4. **Chamomile:** *Chamomilla matricaria*, the scientific designation for chamomile, belongs to the Asteraceae family and is a perennial plant cultivated in North Africa and Western Europe. The chemical components of chamomile encompass flavonoids, including apigenin, patulin, quercetin, and antioxidants such as Kama Zelin, matricin, foreseen, and gallic acid. Additionally, it contains choline, recognized for its anti-inflammatory properties. Chamomile exhibits an anti-spasmodic effect, which aids in alleviating menstrual cramps and decreasing the risk of preterm birth. Furthermore, it stimulates menstruation.
5. **Asparagus racemosus:** *Asparagus racemosus* is the scientific name for Shatavari, which belongs to the Liliaceae family. This plant is predominantly found in the tropical and subtropical regions of India. It comprises glycosides, alkaloids, steroidal saponins, polysaccharides, and mucilage. Shatavari contains

phytoestrogens that help regulate insulin levels in the body. These phytoestrogens also address hormonal imbalances and regulate the ovarian cycle in women. The herb enhances follicle-stimulating hormone levels and promotes folliculogenesis. The primary constituent, saponin, present in Shatavari supports uterine movement and alleviates painful periods. Additionally, Shatavari is utilized in abortion procedures, where it reduces the likelihood of miscarriages and aids in regenerating uterine muscles.

6. **Cocos nucifera:** *Cocos nucifera*, commonly referred to as coconut, belongs to the Agavaceae family and contains flavonoids, polyphenols, and fatty acids. It is primarily found in Southeast Asia and the islands situated between India and the Pacific Ocean. Coconut products are believed to support the structure and function of ovaries, potentially decreasing the size and number of ovarian cysts, thereby contributing to improved hormonal balance. Moreover, coconut-based infusions are esteemed for their anti-inflammatory and antioxidant properties, which can help mitigate hormonal imbalances often linked to PCOS. The healthy fats present in coconut are instrumental in hormone production, which may assist in managing irregular menstrual periods.
7. **Flaxseeds:** Flaxseeds, which are obtained from *Linum usitatissimum* of the Lemnaceae family, have demonstrated potential in the management of PCOS by fostering hormonal balance and enhancing ovarian function. They are composed of omega-3 fatty acids, proteins, dietary fibers, micronutrients, and lignans. Research conducted on a rat model indicates that the hydroalcoholic extract of flaxseeds significantly lowered testosterone levels while elevating progesterone, thereby assisting in endocrine regulation. Furthermore, treatment with flaxseeds resulted in favorable histological alterations in the ovaries, such as an increase in healthy follicles and corpus luteum, along with a decrease in cystic follicles. These findings suggest that flaxseed may aid in the regulation of menstrual cycles and the alleviation of PCOS symptoms, positioning it as a promising natural remedy for this condition [37].

Conclusion

Polycystic Ovary Syndrome (PCOS) is a complex endocrine and metabolic disorder influenced by genetic, environmental, and internal factors. It is characterized by hormonal imbalances, insulin resistance, hyperandrogenism, and chronic inflammation, all of which lead to reproductive, metabolic, and psychological challenges. Prompt recognition of symptoms such as irregular menstrual cycles, hirsutism, acne, and obesity is essential for effective management. Although conventional treatments focus on lifestyle modifications, weight management, and medical interventions, natural remedies like spearmint, ginseng, chaste berry, chamomile, shatavari, coconut, and flaxseeds have shown promising effects in restoring hormonal balance and alleviating symptoms. Continuous research into the pathophysiological mechanisms of PCOS, along with integrative treatment methods, offers hope for improved management strategies and a better quality of life for women affected by this condition.

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