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# Polycystic Ovarian Syndrome: A Comprehensive Review for Female Awareness, Challenges, and Pathways to Solutions

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***Abstract:*** Background: Polycystic ovarian syndrome (PCOS) is a multifaceted condition of the endocrine and metabolic systems. The absence of ovulation, infertility, obesity, insulin resistance (IR), and many ovary cysts commonly identify it. Around 3.4% of the women population (116 million) globally are affected by PCOS, according to estimates by the World Health Organization (WHO). The predisposing factors that increase the chances of PCOS development include genetics, neuroendocrine-related factors, lifestyle, and environmental variables, as well as obesity. These factors can potentially lead to an increase in metabolic syndrome by generating elevated levels of insulin, oxidative stress, excessive production of male hormones, poor development of ovarian follicles, and irregular menstrual cycles. Given the scarcity of completed clinical trials with small sample sizes and limited information on the effectiveness of repurposed drugs for PCOS, it is imperative to conduct additional research and implement meticulously designed clinical trials to shed more light on this matter. This article provides a concise summary of the risk factors and underlying physiological mechanisms involved in anovulation, infertility, and the clinical symptoms and pharmacological therapy options related to the disease PCOS.

***Keywords:*** Ovarian follicles, Insulin resistance, Pharmacological therapy, Polycystic ovary syndrome, Oxidative stress

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## INTRODUCTION

Nowadays, the population is growing exponentially worldwide. As the population increases, it results in the need for a healthy life with nutritious food, wear, and shelter. Unfortunately, the frequency of various diseases also increases with the increase in population. In developing countries, the health of females is a major issue due to several chronic diseases. The alarming rate of unhealthy females demands a worldwide challenge to discover novel and cost-effective sources for health check-ups, treatment, and needed drugs. The reproductive stage is crucial in a female's life, as it alters the body's morphology. A dysregulation might harm her health. However, in reproductive age, females affected with PCOS are due to severe hormonal disorders, mainly contributing to an epidemic of chronic diseases linked to their lifestyles globally (1). PCOS is a disorder often associated with endocrine gynaecology, ovarian enlargement and dysfunction, elevated androgen levels, and resistance to insulin, dyslipidemia, obstructive sleep apnea, depression, and anxiety, cardiovascular diseases, psychological diseases, and other health problems (2). Moreover, in 1990, the WHO included 'E28.2 polycystic ovarian syndrome' with sclerocystic ovary syndrome and Stein-Leventhal syndrome as synonyms among the disorders of ovarian dysfunction included in the International Classification of Diseases, 10th revision (ICD10) (3). However, it has been reported that roughly 10% of women experience PCOS, and nearly 200 million females globally before menopause struggle with its complications. Approximately 6%-21% of the population worldwide develops PCOS (4), depending on the area, ethnicity, and diagnostic standards utilised. In 2017, 1.55 million newly identified cases of PCOS were reported in females belonging to the reproductive age group globally, with 17.23% of these occurrences being females aged 21 to 30. Over the last 30 years, a notable rise in age-standardised incidences of PCOS in the Asian continent has occurred. This review discusses the definition, clinical manifestations, diagnosis, treatment, prognosis, preventive measures, and recent advances in PCOS.

## PATHOGENESIS

### Androgen Abnormalities/Androgen Excess

Near about 6-8/10 females affected by PCOS have high levels of testosterone circulation, and approximately a quarter have high levels of prasterone sulfate (DHEAS). This provides the conclusion for discoverer's to hypothesise that abnormal steroidogenesis may be the primary defect in this disorder. Moreover, the patients suffering from PCOS disorder, many steroidogenic enzymes are raised both in expression and activity by thecal cells; such hyperactivity might result from disruption of signalling pathways inside the cell, which were not found to be involved in its pathogenesis (5,6).

### Ovulatory Abnormalities and Polycystic Ovaries

The development of ovarian follicles is a complex and intricate process. It involves the transition of primordial follicles into a cohort of developing follicles, culminating in the selection of a single antral follicle for ovulation. In PCOS, a triad of ovarian hyperandrogenism, hyperinsulinemia, and abnormal paracrine signalling within the ovary acts as a wrecker to disrupt normal follicular growth. The follicular maturation arrest in PCOS shows a bigger clinical picture, including small antral follicle accumulation at the periphery of polycystic ovaries, irregular menses, and subfertility due to lack of ovulation. The higher output of insulin contributes to premature follicle luteinisation by promoting the enhanced differentiation of granulosa cells in response to follicle-stimulating hormone (FSH) action, which causes the arrest of proliferating activity of granulosa cells and eventually leads to follicle growth (7).

 

**Gonadotropin Abnormalities**

Abnormal maps of gonadotropin pulsatility can be observed in females suffering from PCOS. Specifically, there is normal production of FSH and higher production of LH. This contributes to an abnormal circulation of LH and FSH in the pituitary, particularly in patients of normal weight. The abnormal secretion pattern is further intensified during gonadotropin-releasing hormone challenge tests, leading to increased levels of 17-hydroxyprogesterone and LH in females suffering from PCOS disorder (6). These outcomes provide the conclusion that there is a potential defect in the hypothalamic-pituitary axis in PCOS patients. The abnormality in gonadotropin release associated with PCOS may be an outcome of abnormal adrenal cortex or ovarian steroid release.

**Abnormalities Of Folliculogenesis**

Healthy ovaries typically contain fewer primary, secondary, and small antral follicles as compared to ovaries affected by PCOS. In fact, PCOS ovaries can have 2-6 times more of these follicles. Interestingly, the specific reason for this increased follicle count remains unresolved, but sufficient evidence suggests that abnormal androgen signalling may play a major role. Additionally, research has found a positive relationship between follicle count and levels of testosterone hormone and androstenedione in the blood of affected females (6,8). However, in anovulatory females suffering from PCOS, the growth of antral follicles ceases once the follicle achieves a size of less than 10 mm in diameter, just before the emergence of a primary follicle. Insulin and LH, or both, excessively stimulate the cells of the follicles with a hyperandrogenic environment and result in follicular arrest (8). The relationship with hyperinsulinemia, anovulation and IR in females with PCOS leads to the exploration of insulin sensitisers like metformin drugs as a therapeutic method to stimulate the ovulation process (4,6).

**Insulin Action Abnormalities/Insulin Resistance**

Insulin resistance (IR), usually observed in women suffering from PCOS, often exceeds what would be expected based on their body mass index (BMI). Approximately 50-70% of these females exhibit IR, as determined by various evaluations. This IR leads to compensatory hyperinsulinemia, which is responsible for multiple characteristic properties of PCOS. However, the maximum number of females suffering from PCOS consists of standard or increased insulin secretion, predominantly from those having a family history of suffering from type 2 diabetes, abnormality in β-cell functioning or a lower disposition index (an index that considers insulin resistance) (9). Figure 1 shows the factors that contribute to PCOS pathogenesis. However, accurately assessing insulin resistance is challenging due to the faulty correlation between surrogate measures, such as increasing glucose and insulin levels, and gold standard methods like the euglycemic clamp.

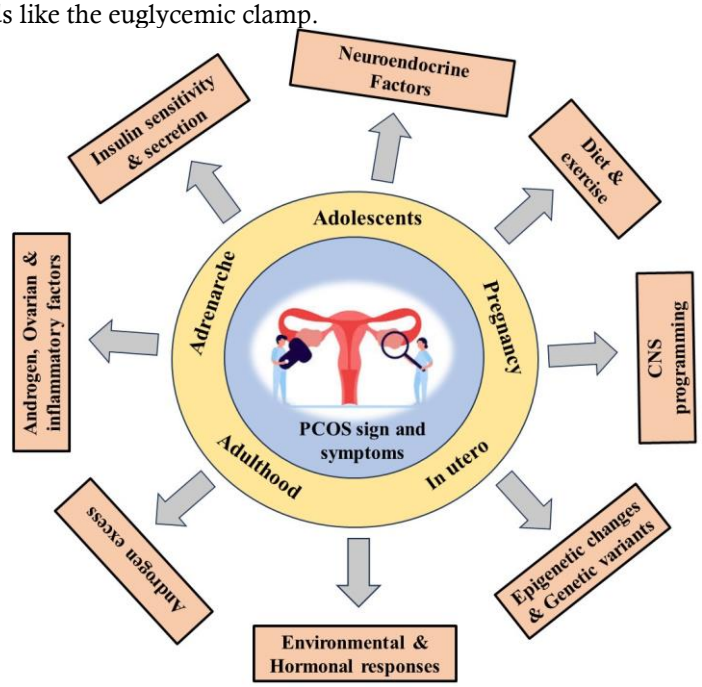


**Fig. 1. FACTORS CONTRIBUTING TO PCOS PATHOGENESIS**

**Obesity And Adipose Tissue Dysfunction**

Females suffering from PCOS have a higher chance of having obesity-related problems as compared to healthy women of the same age, as observed at referral centres (8). Interestingly, the rate of IR in PCOS is much more significant than predicted based on sole BMI; however, only a few females with PCOS are affected by obesity. Moreover, several studies revealed primary defects in insulin or lipolysis regulated in adrenergic tissue in lipocytes (in some cases fibroblasts and myocytes), GLUT4 production, and insulin-mediated glucose transport in females

 

suffering from PCOS, despite proper binding of insulin to its receptor (8,9). However, these discussed abnormalities in insulin action appear to be due to disrupted intracellular signalling of insulin or the influence of factors, including paracrine, autocrine, and endocrine. Moreover, researchers may discover new targets for therapeutic interventions for PCOS and related disorders by gaining a deeper understanding of the mechanisms contributing to the role of adipose tissue abnormalities and IR in females with PCOS (4).

**Intrauterine Environment**

Polycystic ovarian syndrome (PCOS) develops through epigenetic changes during fetal life. Various studies conducted on human beings, monkeys, and sheep have shown ovarian follicular proliferation at birth, and prenatal testosterone excess, whether induced experimentally or occurring naturally, leads to permanent PCOS-like phenotypes. This is further supported by the elevated prevalence in females suffering from PCOS with classical congenital adrenal hyperplasia and virilising tumours. Additionally, they experience intrauterine growth restriction, followed by compensatory growth after birth. However, clinical investigations have not found evidence that high testosterone during the early stages of human development leads to PCOS after birth. Several hypotheses explain the role of the critical period during baby development, when a higher amount of androgen leads to various developmental stages. One study found that umbilical venous blood and maternal androgen levels, measured at different gestational stages, failed to identify the progression of PCOS in adolescents. Moreover, small-scale investigations on the baby's blood levels at term yielded disputed outcomes (8).

**Genetics**

The syndrome known as PCOS affects a significant percentage of first-degree females closely related to the condition, ranging from 20% to 40%. PCOS development is influenced by genetic factors, as indicated by a heritability rate of 0.79 among Dutch twins. Families of females suffering from PCOS also show a genetically transmitted factor that causes hyperandrogenemia, insulin resistance, and insulin secretion, demonstrated by raised DHEAS levels (in male relatives of first-degree relatives), prevalence of IR, metabolic syndrome, and endothelial dysfunction (5). Previous genetic investigations of PCOS have usually utilised individual gene association approaches, where specific gene variants are analysed and genotyped for their relationship with PCOS or its quantitative traits. PCOS is believed to be developed as a common complicated syndrome, similar to conditions of T2DM and inflammatory bowel disease, where multiple genetic variants with moderate effects, along with lifestyle and other factors related to the environment, contribute to the threat. To identify the genes responsible for this complicated disorder, it is crucial to have large sample sizes and to replicate initial findings in independent cohorts. However, some well-published replication research could not explain the initial associations. For example, replication studies for genes encoding of insulin, aldo-keto reductase family 1, member c3 (AKR1C3), cytochrome p450 side-chain cleavage enzyme (CYP11A), and 17β-hydroxysteroid dehydrogenase type 5 gene were not able to replicate the initial associations. On the other side, there have been successful replication studies for specific genes associated with PCOS or its related traits. Fibrillin 3 (FBN3) and 17β-hydroxysteroid dehydrogenase type 6 (HSD17B6) are examples of genes whose association has been replicated. Additionally, there was nominal replication of variants in activin A receptor type IIA (ACVR2A), fem-1 homolog B (FEM1B), and small glutamine-rich tetratricopeptide-containing protein alpha (SGTA) (4). However, advancements in understanding the genetic process of PCOS are slower than those of other common syndromes, such as T2DM, where genome-wide relations have identified several risk alleles in a consistently replicating stage.

**Environmental Factors**

Individuals' lifestyle choices substantially affect the phenotypic expression related to PCOS. Specifically, weight gain is associated with reproductive and metabolic problems associated with PCOS. This is evident through the existence of abdominal obesity, IR, menstrual irregularity, and hyperandrogenism in females with more severe forms of PCOS. On the other hand, weight loss in women affected with PCOS reduces the level of insulin and androgen and shows improvements in dyslipidemia, hirsutism, menstrual and ovulatory dysfunction. However, engaging in mild-intensity exercise, even without weight loss, shows an enhancement in IR and reduces adipose tissue in the body (7). Additionally, it is possible that environmental factors, such as endocrine-disrupting chemicals, can disturb metabolic and ovarian function, resulting in PCOS-like abnormalities. One such chemical is Bisphenol A (BPA), which is widely used as an estrogenic industrial plasticiser and can be detected in most individuals. Research performed on rodents has shown that BPA can increase the formation of ovarian androgens *in vitro* and induce IR *in vivo* conditions. In females affected with PCOS, there is a higher amount of BPA accumulation due to reduced hepatic clearance caused by excess androgen (9).

## CLINICAL MANIFESTATIONS

Symptoms of polycystic ovarian syndrome often initiate during the first menstrual period. Sometimes, the symptoms start later after periods. The typical symptoms and indications of PCOS include:

 

- Irregular, abnormal periods and infertility: Irregular menstruation, characterized by missed, absent, or very heavy menstrual cycles, which can make it difficult to get pregnant.
- Unusual hair growth: Excessive facial, arm, chest, and abdominal hair growth (hirsutism).
- Acne formation: Occurs on various parts of the body, including the back, chest, and face.
- Obesity-related issues: Affects 40%-80% of patients, making it difficult to manage their body weight.
- Darkening of the skin and skin tags: Black skin patches (Acanthosis nigricans) appear, particularly in the groin (the area between the legs), under the breasts, armpits, and neck folds.
- Suffer from thinning hair: Experience hair loss or baldness (9).

**DIAGNOSIS**

The guidelines for defining PCOS have changed over time. The National Institutes of Health (NIH) 1990 conference stated that PCOS should be diagnosed based on oligo-ovulation, clinical or biochemical hyperandrogenism, and the exclusion of other syndromes such as late-onset congenital adrenal hyperplasia and Cushing's syndrome. In 2003, the Rotterdam Consensus expanded the diagnosis to include any two of three features: clinical and/or biochemical hyperandrogenism, oligo-ovulation, and polycystic ovaries (PCO) on ultrasound, after ruling out other endocrinopathies. The Androgen Excess–PCOS Society (2006) recommended that PCOS be defined by the presence of clinical and/or biochemical hyperandrogenism, along with either oligoanovulation and/or PCO, also excluding other related conditions. For evaluation, individualized laboratory testing (table 1) typically includes prolactin, thyroid function tests, SHBG, total testosterone, androstenedione, DHEAS, and 17-hydroxyprogesterone; direct free testosterone assays should be avoided due to poor sensitivity, precision, and reproducibility. AMH is often elevated in PCOS due to increased follicular density and may support diagnosis; however, the 2018 International Evidence-based Guideline advises using validated, population-specific cutoffs rather than AMH as a sole criterion. Obesity is a simple but important clinical parameter, and therapies such as GLP-1 receptor agonists, thiazolidinediones, and combined oral contraceptives, along with supplements like myo-inositol, vitamin D, and synbiotics, can influence SHBG and improve outcomes (9,10,11).

**Table 1. LABORATORY TESTING FOR THE ASSESSMENT OF FEMALES WITH PROBABLE POLYCYSTIC OVARIAN SYNDROME (PCOS) (9,10)**

| Laboratory test | Usefulness |
|---|---|
| TSH<br>Prolactin | For finding thyroid dysfunction and hyperprolactinemia. If detected, re-evaluate for PCOS once the condition is resolved. |
| 17-hydroxyprogesterone (17-OHP) (measured in the follicular phase) | If 17-OHP >6nmol/l, perform an adrenocorticotropic hormone (ACTH) stimulation test. The amount of ACTH-stimulated 17-OHP >10nmol/l is diagnostic of 21-hydroxylase-deficient non-classic adrenal hyperplasia (NCAH) |
| Total and free testosterone | To assess for hyperandrogenemia, consider testing even if there is no clinical indication of hyperandrogenism, when total testosterone or dehydroepiandrosterone sulfate (DHEAS) levels exceed 7 nmol/l or 16 μmol/l. In such cases, evaluation for an androgen-secreting neoplasm is recommended. |
| Luteal phase (22-24 days) progesterone | To evaluate ovulation in hirsutistic patients who claim to have regular menses. |
| 1mg dexamethasone suppression test (DST) or 24h urinary free cortisol | Screening for Cushing syndrome if clinical stigmata are observed. |

Sonographic criteria usually include at least 12 follicles per ovary measuring 2–9 mm and/or an ovarian volume greater than 10 mL, regardless of follicle distribution or stromal echogenicity; meeting criteria in one ovary is enough. Notably, some women with PCOS morphology have regular cycles and no clinical or biochemical hyperandrogenism, and some experts argue that hyperandrogenism should remain a key diagnostic criterion. Research from 2007 shows that women with PCOS, chronic anovulation, and normal androgen levels may not have insulin resistance, challenge the utility of the Rotterdam criteria and support the AE-PCOS view of PCOS as an androgen-excess disorder aligned with NIH. Clinically, women may present with unwanted or excessive hair growth, irregular periods, incidental PCOS on ultrasound, alopecia, and acne. Women with long-standing PCOS are at higher risk of developing other diseases, as shown in Figure 2. Ovulatory dysfunction should be confirmed by clinical or biochemical evidence of oligo-anovulation, such as low midluteal serum progesterone, noting that up to 40% of hirsute women with apparently regular bleeding are oligo-anovulatory (4,9).

 

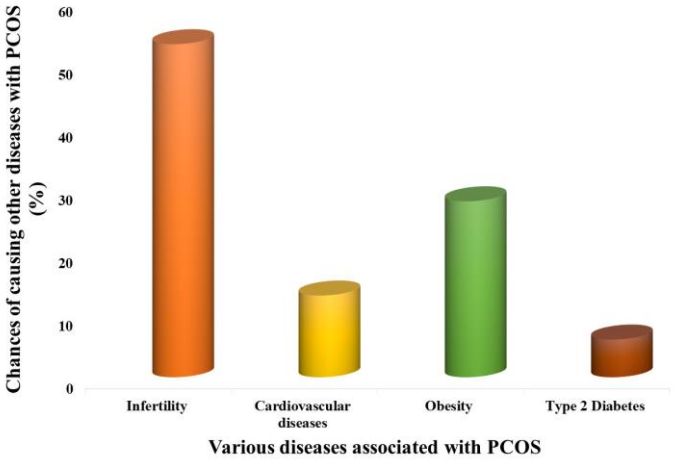


**Fig. 2. VARIOUS DISEASES ASSOCIATED WITH PCOS AND THEIR CHANCE OF OCCURRENCE (12)**

Apart from ovarian morphology, the majority of these characteristics can be identified through history and physical examination. Hyperprolactinemia, non-classic adrenal hyperplasia (NCAH) caused by steroid 21-hydroxylase (CYP21A2) deficiency, and thyroid dysfunction are the other vital disorders to be ruled out. Thyroid-stimulating hormone and serum prolactin levels are used to exclude the latter two disorders (12). An acute adrenal stimulation test is recommended if the 17-OHP level is above 6nmol/l. This test measures 17-OHP levels before and 60 minutes after the intravenous administration of an adrenocorticotropic hormone. However, once the 17-OHP level reaches 30 nmol/L, preferably 45 nmol/L, the diagnosis of NCAH is confirmed. Subsequently, CYP21A2 genetic analysis is performed to validate the diagnosis and determine if the patient carries a serious gene mutation that raises the possibility of a child being born with classic type adrenal hyperplasia (9).

## PROGNOSIS AND HEALTH OUTCOMES

The prognosis for PCOS is primarily dependent on the timely and appropriate management of its symptoms. However, women with PCOS encounter several kinds of symptoms and are often treated by numerous healthcare experts, such as general practitioners, gynaecologists, and endocrinologists. Women with PCOS may encounter issues including infertility, higher risk of heart disease, type 2 diabetes, and mental health problems, including anxiety and depression, as well as body image issues caused by physical symptoms like gaining weight, hirsutism, and acne. Likewise, nutritional intervention or the synergistic effect of diet and supplementation with probiotics, prebiotics, or synbiotics can enhance bacterial diversity and promote beneficial species, such as *Bifidobacterium* and Lactobacillus, thereby contributing to an improvement in the clinical scenario for females affected by PCOS. Females with PCOS are frequently advised to seek cognitive behavioural therapy (CBT) and counselling to improve their mental health. PCOS can cause significant long-term health issues, including endometrial cancer, due to unregulated hormonal imbalances. Routine screening and early intervention are essential in mitigating these risks. Therefore, PCOS has significant short-term effects on reproductive health and long-term implications for the development of chronic diseases (13,14).

## TREATMENT: PATHWAY TO SOLUTION

Polycystic ovarian syndrome (PCOS) is a complex syndrome that impacts several organ systems and has notable effects on metabolism and reproduction. The approach utilised to treat every person should be tailored to their specific signs, symptoms, and desire to conceive. Table 2 provides an overview of the medical equipment and drugs utilised to address the different signs and symptoms of PCOS, along with their potential side effects.

**Table 2. DRUGS UTILISED FOR THE TREATMENT OF PCOS (11)**

| Medication or device | Description | Manifestations treated | FDA pregnancy classes | Major negative issues | Typical dosage | Cost* of drugs |
|---|---|---|---|---|---|---|
| Clomiphene † | Ovulation induction agent, selective estrogen receptor | Infertility (first-line therapy) | X | Multiple pregnancy or ovarian hyperstimulation, thromboembolism, visual disturbances | 50 to 100 mg once in a day | 100 mg for $15 (5-day supply) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | modulator | | | | | |
| Eflornithine (Vaniqa)‡§ | Prevents growth of hairs | Mild hirsutism (second-line therapy) | C | Mild skin irritation | 13.9% Eflornithine cream was applied to the affected part of body twice daily | $78 (brand) for 130-g tube |
| Finasteride (Proscar)‡ | Inhibitor of 5-alpha-reductase | Hirsutism (less recommendation due to inconsistent results) | X | Hypersensitivity reaction decreased libido | 5 mg once in a day | $273 (brand) and $10 (generic) |
| Flutamide‡ | Non-steroidal anti-androgen used mostly for prostate cancer | Hirsutism (effective and safe according to low- to very low-quality evidence) | D | Liver toxicity, thrombocytopenia, leukopenia and hot flashes | 250 mg once or twice in a day | $32 for 250 mg per day |
| Hormonal contraceptives (e.g., pill, vaginal ring, patch)‡ | - | Menstrual irregularities, hirsutism, acne (first-line therapy) | X | Thrombophlebitis, headache, spotting, nausea, and deep venous thrombosis may manifest in individuals. | Varies | Varies |
| Letrozole (Femara)‡ | Non-steroidal competitive inhibitor of aromatase; inhibits production of adrenal androgens | Infertility (first-line therapy) | C | Osteoporosis, thromboembolism, MI, hot flashes, arthralgias | 2.5 to 7.5 mg one time for 5 days | 2.5 mg per day cost $8 (generic) and $128 (brand) |
| Levonorgestrel-releasing intrauterine system (Mirena)‡ | Intrauterine device | Endometrial, hyperplasia, bleeding of uterine in abnormal way (FDA approved) | X | Amenorrhea, nausea, vomiting; infrequent complications include the device entrenched in the myometrium and uterine perforation | 5 years | $815 (not including cost of placement) |
| Metformin‡ | Sensitive for Insulin | Insulin resistance (first-line therapy), Menstrual irregularities (second-line therapy added to hormonal contraceptives), hirsutism (third-line therapy added to hormonal contraceptives and spironolactone) | B | Gastrointestinal upset, lactic acidosis, elevation in homocysteine levels | 1,500 to 2,250 mg once in a day | $4 for 1 g mg twice a day |
| Spironolactone‡ | Antiandrogenic antimineralocorticoid | Hirsutism (second-line therapy added after 6 months of oral contraceptive therapy if not improved) acne (second-line therapy) | C | Hyperkalemia, nausea, breast tenderness | 50 mg one in a day but can be exceeded up to 100-200 mg of dosage | $15 for 100 mg daily |

{**NOTE: *-**Estimated retail price for treatment of 30 days. †-FDA approved for women infertility occurred due to PCOS. ‡-Non FDA-approved for the treating manifestations of PCOS. §- Non-investigated, especially in females

affected with PCOS; thus, the efficacy is not known. ||-Based on mostly anecdotal evidence.}

Treatment goals, such as addressing infertility, regulating menstrual cycles to protect the endometrium, and managing hyperandrogenic symptoms like hirsutism and acne, should align with the patient's preferences to ensure that therapy choices align with their desired outcomes (11,14). Various alternative therapies for curing PCOS are discussed below:

**Drug Repurposing in PCOS**

Drug repurposing, also called drug repositioning or drug re-tasking, involves finding novel applications for medicines that the USFDA has previously authorised for specific therapeutic purposes (15). Exploring alternative drugs, particularly those used in diabetes treatment, could provide a better understanding of potential novel therapeutics for females with PCOS-related complications. Metformin, a medication belonging to the biguanides category, is typically prescribed alongside first-choice drugs (COCs) to regulate the ovulation cycle in females affected with PCOS (having the ability to improve insulin sensitivity). Agents such as clomiphene citrate and/or aromatase inhibitors are used for ovulation induction in these cases. It is also observed that many COC agents can cause nausea, vomiting, depression, headaches, and migraines. Furthermore, spironolactone, a commonly prescribed medication for androgen-related complications, has the potential to cause hyperkalemia (15).

**Surgery**

**Bariatric surgery (BS)**

Recently, Bariatric surgery has been honoured as a promising process for weight loss in persons with severe obesity. When traditional methods of diet and physical activity fail to produce substantial loss of body weight, bariatric surgery becomes a viable option. The main types of procedures performed are restrictive and combined restrictive and malabsorptive strategies, including adjustable gastric banding and Roux-en-Y gastric bypass. It is not surprising that in research conducted on 17 women with PCOS and an estimated body mass index of 50.7 $kg/m^2$, bariatric surgery led to an impressive average weight loss of 41 ± 9 kg within a span of 12 months. However, females undergoing BS are at higher risk of experiencing nutritional deficiencies, such as protein, vitamin $B_{12}$, folate, vitamin D, iron, and calcium (16).

**Laparoscopic ovarian diathermy**

Compared to gonadotropins, laparoscopic ovarian diathermy (LOD) has been reported lesser incidence of multiple gestation. Based on several investigations, there is no substantial variance in miscarriage or live birth rates between females with clomiphene-resistant PCOS who undergo LOD versus those who receive gonadotropin therapies. LOD is highly beneficial in females with elevated LH levels, as it significantly reduces LH and androgen levels after surgery. In 63%-85% of females, LOD re-establishes the menstrual cycle, and the beneficial effects on reproductive results can last for several years (16).

**PREVENTATIVE MEASURES**

Preventing females affected by PCOS depends on managing its various symptoms. These include infertility due to ovulatory dysfunction, menstrual irregularities, and androgen-related symptoms. Figure 3 illustrates the preventive measures for PCOS. The following are some of the key strategies to consider:

**Weight Loss and Diet**

Gain of body weight in females with PCOS, particularly in the abdominal area, is attributed to elevated levels of androgenic hormones. This often results in an apple-shaped body rather than the typical pear-shaped character. The initial step for women with PCOS is to focus on weight loss and restrict calorie intake. Various studies have proven that even a slight reduction of 5% to 10% in body weight can help recover normal menstrual cycles in females. An optimal diet would prioritise fibre-rich foods while minimising intake of saturated fats and carbohydrates. Low glycemic index carbohydrates should be the focus, including nutrient-dense options such as broccoli, raw carrots, lentils, soy, bran breakfast cereals, and whole-grain bread (15).

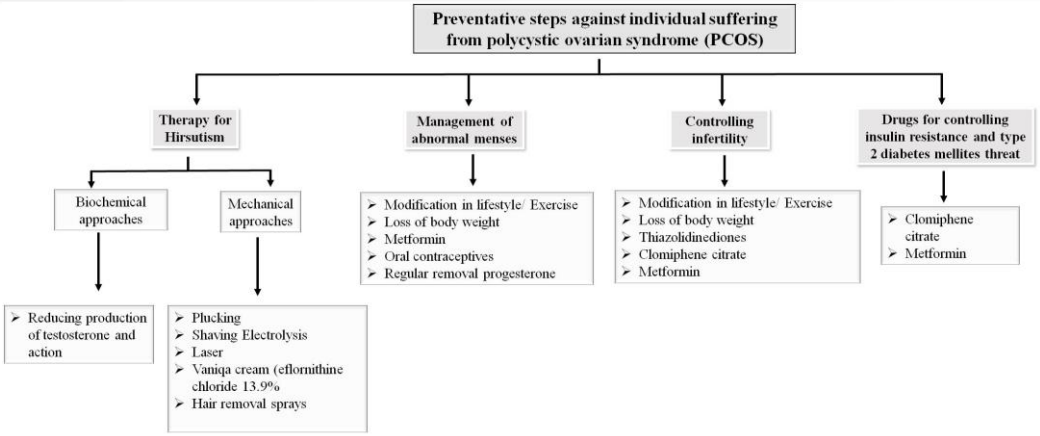


**Fig. 3. SHOWING THE PREVENTIVE MEASURES FOR PCOS (11)**

**Complementary and Alternative Medicine (CAM)**

The current care and available drugs for PCOS have only moderate effectiveness, and some patients remain untreated even with both non-pharmacological and pharmacological therapies. According to certain publications, pharmacologically-based treatments are helpful in only 60% of sufferers. CAM is a widely recognized method used by over 70% of PCOS patients during their illness. The National Center for Complementary and Integrative Health (NCCIH) classifies complementary methods into three categories based on their main therapeutic input: nutritional, psychological, physical, or a combination of these (15). Previous studies have explored various CAM methods, such as traditional Chinese medicine (TCM), immunotherapy, diet therapy (including herbal and medicinal foods, probiotics, and vitamin or supplement therapy), psychotherapy, spa treatments, yoga, tai chi, and oxygen therapy as promising approaches to reduce the severity of PCOS and its associated problems.

**Acupuncture Approach**

For more than 3 millennia, acupuncture has been an integral component of complementary and alternative medicine (CAM) in China. This practice involves the insertion of thin needles into the skin and muscles for the purpose of sensory stimulation. By initiating the somatic afferent nerves in the skin and muscles, acupuncture has been reported to enhance the clinical manifestations of PCOS. It achieves this by regulating the activity of the somatic and autonomic nervous systems, as well as the metabolic and endocrine functions. One notable effect of acupuncture is the increased production of β-endorphins, which in turn impacts the release of gonadotropin-releasing hormone, ovulation, and menstruation. Consequently, acupuncture has the potential to induce ovulation and restore regular menstruation (15).

**Additional Supplementations and Herbs**

Supplementation products, aside from medications approved by the USFDA, are proven beneficial for certain females diagnosed with PCOS. Supplementation items, aside from medications approved by the USFDA, have proven efficacy in certain women diagnosed with PCOS. These products encompass a range of options, including vitamin D supplements, resveratrol, α-lipoic acid, omega-3 fatty acids, berberine, folic acid, myoinositol (MI), and d-chiro-inositol (DCI). Resveratrol, berberine, alpha-lipoic acid, and omega-3 fatty acids, known for their anti-inflammatory, antioxidant, cardioprotective, and neuroprotective properties, stand out as the most highly recommended supplements for managing PCOS. Folic acid is generally prescribed to females with PCOS who wish to conceive, as supported by several studies (15). Zishen Qingre Lishi Huayu recipe (ZQLHR) is a traditional Chinese medicine product that combines nine herbs for the treatment of PCOS. In PCOS patients, ZQLHR therapy and Liquorice (*Glycyrrhiza glabra*) root reduce blood levels of testosterone, insulin, and LH, thereby improving clinical symptoms of obesity and acne, and restoring the menstrual cycle and ovulation. Nicker Bean (*Caesalpinia bonducella*), a medicinal plant, has recently garnered attention for its potential therapeutic effects (anti-androgenic, anti-inflammatory and hypoglycemic) in PCOS.

**Pharmacological Treatments**

Regardless of weight, complaints, or any other factors, it is crucial to provide women diagnosed with PCOS with advice on maintaining a healthy lifestyle. In most cases, particularly in those with low to moderate forms, diet and exercise alone can bring significant benefits to women. However, the treatment approach primarily depends on the female's decisions and overall health. Figure 4 illustrates the genetics and diseases associated with PCOS, as well as its treatment. The healthcare provider can select the most suitable oral contraceptive based on symptoms beyond menstrual abnormality. For instance, Yasmin®, Yaz®, or other similar agents may exhibit anti-androgenic issues,

 

leading to a reduction in androgen production (13).

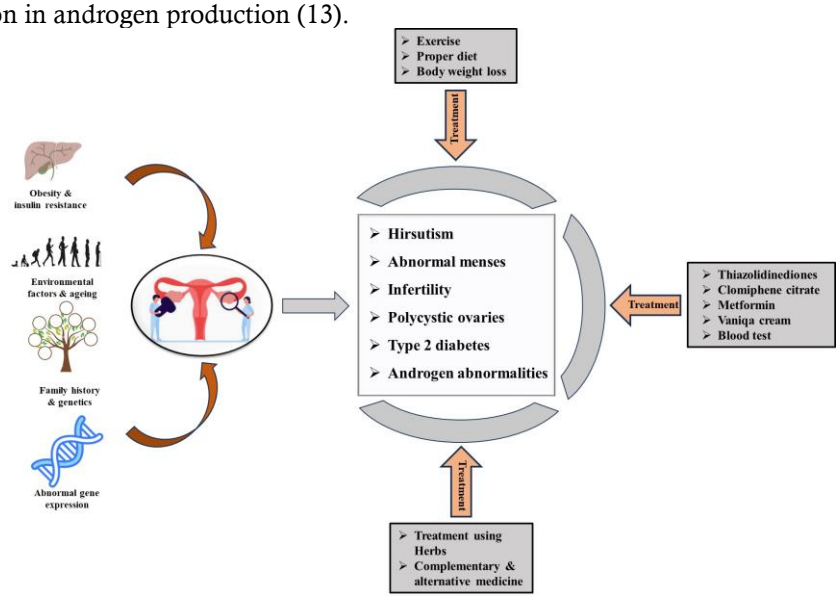


**Fig. 4. SHOWS THE GENETICS, CAUSE, DISEASES ASSOCIATED AND TREATMENT OF PCOS**

**PCOS AMONG ADOLESCENTS**

PCOS might be quite challenging to identify in the adolescent period since its symptoms are common with normal pubertal changes. Menstrual irregularity is a common early sign of PCOS in adolescence. Adolescents exhibiting menstrual irregularities or periodic acne are likely to have PCOS, particularly if they possess a high body mass index. Moreover, timely diagnosis and treatment are critical in avoiding long-term consequences such as type 2 diabetes, metabolic issues, and heart disease. Approximately 70% of females, if irregular menstruation fails to resolve during the first two years after menarche, is associated with metabolic and clinical characteristics of PCOS (13). Although the precise cause of PCOS is unknown, an integration of environmental and genetic factors is believed to be involved in it. Adolescent PCOS management relies heavily on lifestyle therapies like food and exercise because of this metabolic abnormality (4). Depression and anxiety may result from the chronic nature of the illness and its treatment. The females affected by PCOS have more therapeutic alternatives after the arrival of the so-called fourth-generation combined oral contraceptive pill and oral contraceptives that consist of drospirenone with anti-mineralocorticoid and anti-androgenic properties (13).

## RECENT ADVANCES IN PCOS THERAPIES

Polycystic ovarian syndrome (PCOS), a condition that impacts females in their entire lives, cannot be cured but can only be managed to achieve remission. To effectively address PCOS, it is imperative to establish different treatment priorities and goals based on the specific course of the disease rather than relying solely on a single medication.

### Effectiveness of Metformin in the Treatment of PCOS

Along with lifestyle changes, persons with PCOS and metabolic problems may need medical interventions, including metformin drugs or statins (inhibit the activity of HMG-CoA reductase). However, few of the cases suffered from PCOS respond positively to metformin. Several studies have revealed that a combination of inositol with metformin can successfully resolve IR and menstrual cycle regularity in infertile females affected by PCOS. Moreover, recent studies proved that metformin has a negligible impact on clinical rates of pregnancies and childbirths for PCOS females undergoing *in vitro* fertilisation/intracytoplasmic sperm injection (4).

### Managing Excess Androgens

In cases of PCOS individuals with high concentrations of androgens, metformin has been noted to have a negligible effect in reducing androgen concentration in pregnant females suffering from PCOS. However, subgroup analysis did observe a slight decrease in androgen levels in non-obese females affected with PCOS-carrying male foetuses (2). It remains uncertain whether metformin's androgen-lowering effects extend to the cardiovascular system. Therefore, other medications that modulate metabolism, including thiazolidinediones (classic insulin sensitisers) and non-classical insulin sensitivity-improving medicines like acarbose, sodium-glucose cotransporter (SGLT2) inhibitors, and glucagon-like-peptide 1 receptor agonists (GLP-1RA), are also recommended and beneficial for PCOS females. There is additional research indicating that metabolic surgery has a significant impact on curing metabolic problems and hyperandrogenism issues in obese individuals with PCOS.

## CONCLUSION

Polycystic ovarian syndrome (PCOS) is a complex endocrine-related disorder affecting a large number of females belonging to the reproductive age group. A combination of symptoms, such as hyperandrogenism, abnormal menstrual cycles, and polycystic ovarian morphology, characterises the syndrome. The development of PCOS has been linked to a variety of biochemical and environmental factors, making its etiology and pathophysiology complex and multifaceted. Generally, central to the advancement of PCOS are IR, type 2 diabetes, heart-related disease, uterine cancer, and hyperinsulinemia, all of which contribute to the metabolic imbalances and hyperandrogenism observed in affected women. In addition, endocrine-disrupting chemicals (EDCs), including bisphenol A (BPA), have been linked with the pathogenesis of PCOS, especially in adolescent girls. The primary challenge in treating PCOS lies in diagnosis, as different criteria (e.g., the Rotterdam criteria) can lead to variations in prevalence and diagnostic methods. The importance of a comprehensive and interdisciplinary approach to treating women with PCOS is highlighted by the psychological impacts it can have, such as increased rates of anxiety, depression, and body image issues. Although advances have been made in the recognition and treatment of PCOS, significant gaps in knowledge and treatment effectiveness remain. Future research should focus on unravelling the genetic, molecular mechanisms, developing more accurate diagnostic tools, and exploring new therapeutic targets. Additionally, parallel research is necessary for greater clarity regarding the natural history of PCOS and the outcomes associated with various treatment strategies. Ongoing research and collaboration between medical professionals, researchers, and affected females are critical for improving our understanding and management of this common and severe disease.

### DECLARATION OF CONFLICT OF INTEREST

The authors declare that they have no conflict of interest that could have appeared to influence the work reported in this paper.

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