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Review

Understanding PCOS: A Systematic Review of Pathophysiology to Therapeutic Options



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|  | Abstract |
| Published on: 26 Nov 2024 | <p>Polycystic Ovary Syndrome (PCOS) is a multifaceted endocrine disorder affecting 5-10% of women of reproductive age worldwide. Characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, PCOS is a leading cause of infertility, metabolic disorders, and psychological distress. The etiology of PCOS remains unclear, but genetic, environmental, and hormonal factors contribute to its pathogenesis. Clinical manifestations include irregular menstrual cycles, hirsutism, acne, and weight gain. Insulin resistance, type 2 diabetes, and cardiovascular disease are common comorbidities. Early diagnosis and management through lifestyle modifications, pharmacological interventions, and surgical options can improve quality of life and reduce long-term health risks.</p> |
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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a common hormonal condition that affects women, particularly those in their reproductive years. It is marked by an imbalance of reproductive hormones, which can cause irregular menstrual cycles, higher levels of male hormones (androgens), and often, multiple small cysts on the ovaries.

Common symptoms of PCOS include irregular or missed periods, increased hair growth (typically on the face, chest, and back), acne, weight gain, and challenges with fertility. Although the exact causes of PCOS are not fully understood, it is believed to be influenced by a combination of genetic, hormonal, and lifestyle factors, with insulin resistance playing a major role in many cases.

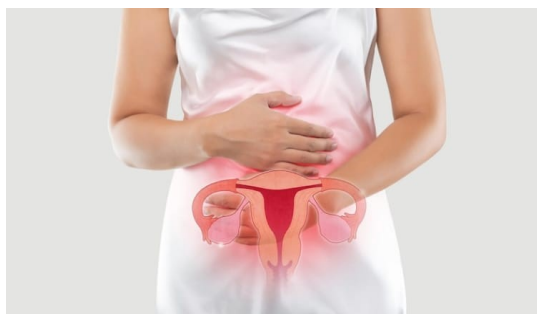
PCOS impacts more than reproductive health alone; it also raises the risk of metabolic issues such as type 2 diabetes and cardiovascular disease. Although there is no cure, lifestyle adjustments, medications, and other treatments can effectively manage symptoms and enhance quality of life for those affected.

Reviewing research articles on PCOS typically involves understanding the etiology, which is multifactorial and influenced by genetic, hormonal, and environmental factors. Studies often focus on the diagnostic criteria—most commonly the Rotterdam criteria—as well as treatment strategies that range from

lifestyle modifications to pharmacological interventions. Current research also explores the syndrome’s molecular basis and its implications for long-term health outcomes.

The syndrome’s impact extends beyond reproductive health, as it is closely associated with metabolic issues that include insulin resistance, obesity, and a heightened risk of developing type 2 diabetes and cardiovascular disease. This interconnection between reproductive and metabolic health highlights the systemic nature of PCOS, emphasizing the importance of understanding it as more than just a gynecological condition.

Current research is also increasingly focused on the molecular basis of PCOS, investigating the roles of genetics, inflammatory pathways, and metabolic signals that contribute to its development. This expanding body of research is crucial for better understanding the long-term health implications of PCOS, which may include chronic conditions such as diabetes, cardiovascular disease, and psychological impacts like anxiety and depression. (1,2,3)



Pathophysiology

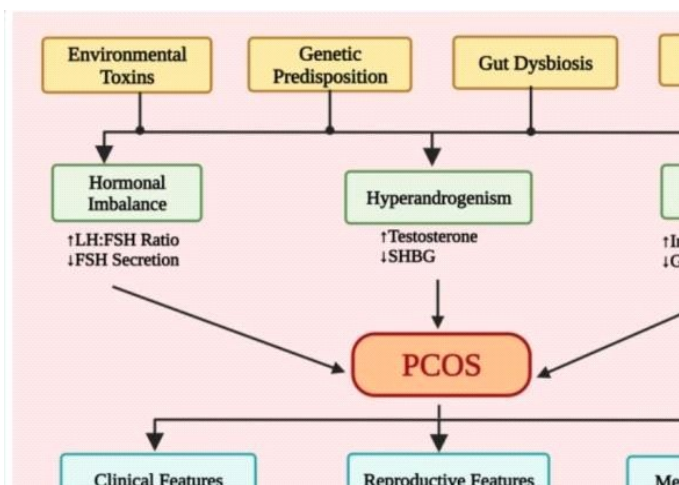
The PCOS Pathophysiology is mainly concerned with hormonal imbalance, chronic low-grade inflammation, hyperandrogenism and insulin resistance, which effects or damages folliculogenesis and also increases the rate of risks which are related to comorbidities such as Type-2 Diabetes and Endometrial cancer.

Hyperandrogenism

The PCOS bio-chemical hallmark is hyperandrogenism which is clinically apparent as acne alopecia and hirsutism. Almost 70–90% of PCOS patients are observed with high levels of androgen with oligo menorrhea. According to the severity of the phenotype their concentration increases frequently. Excessive production of androgen by the ovaries as well as adrenals, contributes to hyperandrogenism. (4). The elevated levels of free testosterone, a key hormone involved in the development of PCOS, serve as indicator of hyperandrogenism.

Hyperinsulinemia

Insulin plays a crucial role in both lipogenesis and glucose homeostasis, acting as a mitogenic hormone that influences carbonate, fat, and protein metabolism. Its effects are mediated through receptors, which are mediated through insulin receptors, which are widely distributed across tissues within the hypothalamic-pituitary-ovarian (HPO) axis. In steroidogenic tissues like the ovary and adrenal cortex, insulin enhances the activity of specific trophic hormones, thereby promoting steroidogenesis. (5)



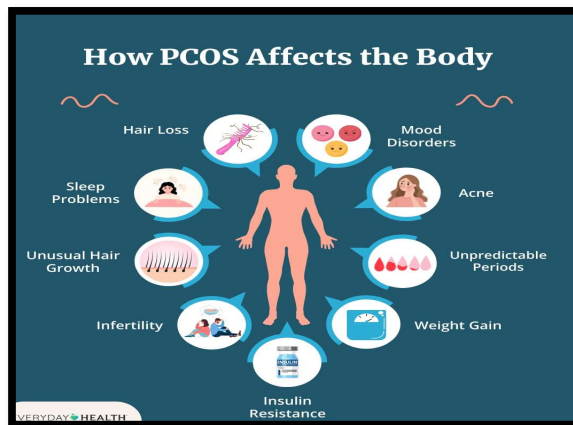
causes and risk factors

While the exact cause of PCOS is unknown, genetics, insulin resistance, common in PCOS, can lead to higher insulin levels that trigger the ovaries to produce more androgens, exacerbating symptoms.

Health implications

PCOS is associated with a higher risk of developing several health issues, including:

- Type 2 diabetes (due to insulin resistance)
- Obesity and related complications
- Metabolic syndrome
- Heart disease
- Endometrial cancer (due to irregular menstruation).



Genetic Factors

Genetic variants: Several genetic variants have been identified, including those affecting androgen receptors, insulin signaling, and follicular development (7,8).

Twin studies: Twin studies suggest a high heritability of PCOS, with estimates ranging from 70% to 90% (9). Family history: PCOS tends to run in families, suggesting a genetic component (6).

Hormonal Imbalance

Hyperandrogenism: Elevated androgen levels contribute to PCOS symptoms, including hirsutism and acne (10).

Insulin resistance: Insulin resistance and hyperinsulinemia exacerbate androgen production and contribute to metabolic complications (11).

Estrogen-progesterone imbalance: Altered estrogen- progesterone ratios disrupt ovulation and contribute to PCOS symptoms (12).

Environmental Factors

Obesity: Obesity exacerbates insulin resistance, hyperandrogenism, and metabolic complications in PCOS (13).

Diet: A diet high in refined carbohydrates and saturated fats contributes to insulin resistance and metabolic complications (14).

Stress: Chronic stress may contribute to hormonal imbalances and PCOS symptoms (15).

Other Factors

Fetal development: Intrauterine exposure to androgens may program PCOS development.

Epigenetics: Epigenetic modifications, such as DNA methylation, may contribute to PCOS pathogenesis.

Gut microbiome: Alterations in the gut microbiome have been linked to PCOS, potentially contributing to metabolic and hormonal imbalances.

Diagnosis

Diagnostic criteria

NICHD/NIH Criteria [1990]

- Hyperandrogenism.
- Oligo-ovulation/Anovulation.
- Exclusion of other related disorders. (16)

ESHRE/ASRM Rotterdam Criteria [2003]

- Hyperandrogenism
- Oligo-ovulation/Anovulation
- Polycystic Ovaries (17)

Androgen Excess Society [AES] Criteria [2006]

- Hyperandrogenism
- Oligo-ovulation/Anovulation
- Polycystic Ovaries
- Exclusion of other related disorders. (18)

Clinical features

Hyperandrogenism: Hirsutism, Acne, Male pattern baldness. (19)

Ovulatory Dysfunction: Oligo menorrhea, Amenorrhea. (20)

Polycystic Ovaries: Presence of less than 12 follicles per ovary.(21)

Laboratory tests

Hormonal Assays: Testosterone, LH/FSH ratio. (22)

Glucose Metabolism: Fasting glucose, Insulin levels. (23)

Lipid Profile: Cholesterol triglycerides. (24)

Imaging studies

Pelvic Examination: Polycystic Ovaries, Ovarian Volume. (25)

Treatment

Pharmacological treatment

Hormonal Contraceptives

- Ethinyl estradiol + cyproterone acetate (Diane-35): 80-90%effective in reducing hirsutism(26)
- Ethinyl estradiol + drospirenone (Yasmin): 70-80% effective in improving acne and hirsutism (27)

Fertility Medications

- Clomiphene citrate: 60-80% effective in inducing ovulation (28)
- Letrozole: 70-90% effective in inducing ovulation (29)
- Gonadotropins (e.g., FSH): 80-90% effective in inducing ovulation(30)

Anti-Androgens

- Spironolactone: 60-80% effective in reducing hirsutism (31)
- Finasteride: 50-70% effective in reducing hirsutism (32)

Insulin Sensitizers

- Metformin: 50-70% effective in improving insulin sensitivity and reducing androgen levels(33).
- Pioglitazone: 40-60% effective in improving insulin sensitivity (34)

Other Medications

- Flutamide: 50-70% effective in reducing hirsutism (35)
- Norethindrone: 40-60% effective in reducing menstrualirregularities (36)

Please note that effectiveness percentages may vary depending on individual studies and patient populations.

Non-pharmacological

Lifestyle Changes

- Regular exercise: Improves insulin sensitivity and hormonebalance(37)
- Weight management: Maintains healthy weight to reducesymptoms(38)
- Stress management: Yoga, meditation, and deep breathingexercises(39)
- Sleep hygiene: 7-8 hours of sleep per night (40)

Dietary Modifications

- Balanced diet: Whole foods, fruits, vegetables, whole grains (41)
- Low-carb diet: Reduces insulin resistance (42)
- Omega-3 rich foods: Fatty fish, flaxseeds, and walnuts (43)
- Probiotics: Supports gut health and hormone balance (44)

Natural Supplements

- Omega-3 greasy acids: Diminishes aggravation and makes strides hormone adjust (45)
- Vitamin D: Directs menstrual cycles and richness (46)

- Berberine: Moves forward affront affectability and hormone adjust (47)
- Saw palmetto: Pieces androgen receptors, lessening hair development (48)
- Turmeric/Curcumin: Anti-inflammatory properties (49)
- Ginger: Decreases irritation and moves forward affront affectability (50)
- Cinnamon: Brings down blood sugar and makes strides affront sensitivity

D. Herbal Remedies

- Chasteberry (*Vitex agnus-castus*): Directs menstrual cycles.
- Peony (*Paeonia lactiflora*): Progresses hormone adjust and fertility.
- Licorice root (*Glycyrrhiza glabra*): Decreases androgen levels.

Recent advances in the management of PCOS

PCOS is recognised as a heterogeneous condition, with initial management depending on the specific clinical issues present, such as anovulation or hirsutism.

Hirsutism

The primary approach to managing PCOS often focuses on hair removal methods. In some cases, these methods remain a preferred treatment option even for women seeking to conceive. Anti androgen therapy, introduced in the 1960s, has been effective in treating symptoms of hyperandrogenism, including hirsutism and acne. Medications such as Spironolactone, cyproterone acetate, and more recently flutamide are commonly used.

Anovulation

The use of human pituitary follicle-stimulating hormone (FSH) to introduce ovulation in anovulatory women began in 1958 but was discontinued due to high complication rates for both mothers and fetuses. In 1961, Greenblatt and colleagues successfully demonstrated ovulation induction using clomiphene citrate, a drug chemically related to the non-steroidal estrogen chlorotrianisene. Clomiphene citrate became a favored option due to its low cost, low toxicity and minimal side effects.

Weight loss

In contemporary society, changes in dietary habits have contributed to increased obesity among women, which exacerbates PCOS symptoms, as excess body fat heightens insulin resistance. Obese women with PCOS typically experience irregular ovulation and hyperandrogenism, making treatment less effective. However, weight loss can lead to significant improvements in managing the condition. [51]

Recent medicines used in regulating pcos :

Oral Contraceptives are Commonly prescribed worldwide to help regulate PCOS Symptoms, particularly for managing hirsutism, Acne and Irregular menstrual cycles. These pills are formulated with hormones that initiate an artificial menstrual cycle, allowing for regular withdrawal bleeding. Typically, contraceptive pills are packaged with 21 active tablets, followed by seven inactive tablets to prompt a week long break from the medication. These contraceptives also effectively reduce excess hair growth and acne due to their small dose of male hormone blockers, which significantly lower free testosterone levels in the body. During their use, pregnancy is effectively prevented. Various Brands of these contraceptive pills are widely available in the market, each offering Similar benefits for managing PCOS Symptoms.

They are:

1. Dioune-35 (Contain small amount of synthetic progestin CPA).
2. Yasmin (Have small amount of synthetic progestin).
3. Marvelon
4. Femoden-ED
5. Microgynon

Some medications containing cyprosterone acetate (CPA) are highly effective for managing Severe androgen-excess disorders. CPA acts as an androgen-blockers, which helps to reduce the ovarian production of testosterone. Additionally, as a progestin, CPA offers protective benefits for the uterus, lowering the risk of cancer and helping to lighten menstrual periods. CPA is typically prescribed alongside estrogens to enhance its therapeutic effects. [52]

CONCLUSION

Polycystic Ovary Syndrome (PCOS) is a complex and multifaceted endocrine disorder affecting millions of women worldwide. Characterized by hormonal imbalances, ovulatory dysfunction, and metabolic

complications, PCOS has significant impacts on reproductive, physical, and mental health. While the exact causes of PCOS remain unclear, research highlights the interplay of genetic, environmental, and lifestyle factors. Effective management of PCOS requires a comprehensive approach, incorporating lifestyle modifications, dietary changes, and evidence-based medical interventions. Early diagnosis, individualized treatment plans, and ongoing support can significantly improve quality of life, fertility outcomes, and long-term health prospects for women with PCOS. Further research is essential to unravel the pathophysiology of PCOS, develop more targeted therapies, and address disparities in diagnosis and care. By promoting awareness, education, and multidisciplinary collaboration, we can enhance the well-being and empowerment of women living with PCOS.

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