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POLYCYSTIC OVARY SYNDROME: DECODING THE COMPLEXITIES OF PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT

Mr. Prathik G R* Department of Pharmacy Practice, Karavali College of Pharmacy, Vamanjoor (post), Manglore, Karnataka, India- 575028 *Corresponding Author

Ms. Hiba Muneer Department of Pharmacy Practice, Karavali College of Pharmacy, Vamanjoor (post), Manglore, Karnataka, India- 575028

Dr. Sheik Farhad Ahamed Department of Urology Yenepoya Medical College Hospital, Derlakatte, Mangalore, Karnataka, India- 575018

Mr. Thanveer Ahammed Chonari Junior Research Fellow, Ph D Scholar Yenepoya University, Mangalore, Karnataka, India- 575018

ABSTRACT

The prevalence of Polycystic Ovary Syndrome (PCOS) among women of reproductive age globally ranges from 5% to 26%, with multifaceted clinical manifestations. This article delves into the pathophysiology, diagnosis, and treatment strategies for PCOS, focusing on adolescents. The pathophysiology of PCOS involves ovarian cell abnormalities, genetic and ethnic influences, and dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis. Additionally, hyperandrogenemia plays a crucial role, contributing to a self-sustaining cycle of hormonal imbalance and complications such as hypertension. Diagnosing PCOS is challenging due to overlapping symptoms with normal pubertal changes, necessitating a comprehensive evaluation and adherence to diagnostic criteria, including polycystic ovarian morphology, irregular menstrual cycles, and hyperandrogenism. Treatment approaches encompass lifestyle modifications emphasizing psychological support, medication like oral contraceptives and metformin, and individualized therapies targeting symptom management and metabolic concerns. Cosmetic interventions and fertility treatments may also be employed, with lifelong follow-up crucial for optimal management and addressing psychological comorbidities. This comprehensive approach aims to improve long-term outcomes and quality of life for adolescents affected by PCOS, underscoring the importance of multidisciplinary care and personalized treatment plans.

1. INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting 5% to 26% of reproductive-age women. Despite its name, PCOS involves abnormal ovarian follicles rather than true cysts. Key features include hyperandrogenism, insulin resistance, and oligo-/anovulation, which contribute to symptoms like irregular menstruation, elevated testosterone, and enlarged ovaries[1-4]. Genetic predisposition, hyperinsulinemia, and neuroendocrine abnormalities are implicated in its pathogenesis[5-7]. PCOS increases the risk of infertility, type 2 diabetes, cardiovascular disease, and metabolic syndrome[8-10]. Diagnosis is challenging, particularly in adolescents, due to overlapping pubertal changes[11-12]. Two main diagnostic criteria are used: the 1990 NIH and the 2003 Rotterdam criteria, both focusing on hyperandrogenism and ovulatory dysfunction. Treatment focuses on lifestyle changes and medications targeting hyperandrogenism, ovulatory dysfunction, and insulin resistance, with bariatric surgery considered in severe cases[14-20].

2. Pathophysiology

A complex disorder including neuroendocrine, metabolic, and ovarian dysfunctions, PCOS induces a self-sustaining cycle of pathological alterations. PCOS is primarily thought to be caused by abnormalities in ovarian cells, specifically theca cells, which lead to excessive production of androgens, even if its exact etiology is yet unknown. Its frequency is influenced by genetic and ethnic variables, such as those seen in Mexican, Native American, and Spanish populations. The pathophysiology of this condition is further complicated by key anomalies such as insulin resistance, elevated Gonadotropin hormone-releasing hormone (GnRH) pulsatility, and a high LH to FSH ratio, as reported by Stein and Leventhal[5-6].

A key component of PCOS pathogenesis is the disruption of the hypothalamic-pituitary-ovarian (HPO) axis. Increased pituitary sensitivity to GnRH may be the cause of elevated LH pulsatility, which selectively suppresses FSH release and messes with normal follicular development. The illness is made worse by hyperandrogenaemia's feedback on the HPO axis, which feeds the cycle of hormonal imbalance. The classic view of PCOS as exclusively an ovarian condition has been expanded by recent research, which emphasizes the major contribution of neuroendocrine dysfunction to PCOS pathogenesis. While the entire pathophysiology of PCOS is still not fully understood, several processes may contribute to the development of hypertension in PCOS[8-10].

The pathophysiology of PCOS includes dysregulation of the ovary and liver, which leads to an increased synthesis of lipids, insulin, androgens, estrone, and LH. As PCOS progresses, hyperandrogenaemia becomes a key component that affects the severity of the condition. The complex pathophysiology of PCOS is influenced by fat buildup, insulin resistance, hyperinsulinemia, imbalances in the LH-to-FSH ratio, and increased estrogen levels. The intricate network formed by these nonlinearly interacting elements exacerbates the symptoms of PCOS[11]. Theca and granulosa cells interact during steroidogenesis, with theca cells generating ovarian androgens that are then converted to estrogens in granulosa cells upon stimulation by FSH[12].

PCOS is linked to metabolic issues like dyslipidemia, obesity, hypertension, and type 2 diabetes, causing kidney disease marked by changes in creatinine and eGFR. Elevated creatinine and hyperfiltration suggest glomerular injury and vascular dysfunction. Folic arrest in PCOS results from imbalances in androgens, FSH, and AMH, disrupting the balance between dormant and developing follicles. Elevated LH prompts theca cells to produce androgens, but low FSH and androgen-to-estradiol conversion prevent dominant follicle selection, leading to persistent anovulation. AMH,

released by granulosa cells, hinders primordial to primary follicle transition, causing many small follicles to stop growing, creating the typical polycystic appearance[14].

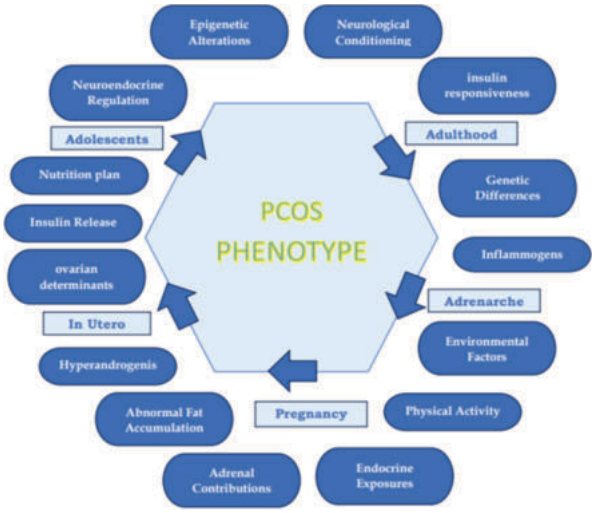

Figure 1: Factors contributing to its phenotype, shaping the disorder across a woman's life cycle. These factors, depicted in circles, potentially impact the pathophysiology of PCOS, representing a biological network influenced by neuro-endocrine, hormonal, metabolic, genetic, and environmental interactions[5].

In healthy females, the adrenal glands and the ovaries, in reaction to Adrenocorticotropic Hormone (ACTH) and Luteinizing Hormone (LH), respectively, release androgens. The adrenal glands may occasionally be involved in PCOS, despite the ovary being the main source of androgens. This is indicative of abnormal gonadotropin secretion with excessive mean LH, low or low-normal FSH, and a chronically high frequency of GnRH pulse secretion. The patho-physiology of PCOS is further complicated by hyper-androgenaemia, which interferes with the normal steroidal control of gonadotropin secretion and GnRH[15].

3. Clinical Manifestation

The three main clinical signs of androgen excess in polycystic ovarian syndrome (PCOS) are irregular menstruation, moderate to severe inflammatory acne, and hirsutism. It is important to separate hirsutism—which is defined as excessive terminal hair development in male-typical body areas—from hypertrichosis, which is a word for generalized increased body hair growth that can be brought on by certain medications or genetic conditions. Clinical hyper-androgenism, such as hirsutism, acne, or alopecia, as well as menstrual irregularities, such as oligomenorrhea, primary or secondary amenorrhea, irregular periods, and heavy menstrual flow, are clinical characteristics of polycystic ovarian syndrome (PCOS). Stein and Leventhal reported menstrual irregularity and infertility in PCOS in 1935, recommending ovarian wedge resection for improvement. Diagnostic tests may identify metabolic disorders, such as insulin resistance, glucose intolerance, obesity and dyslipidemia, on blood testing and/or polycystic ovarian morphology (PCOM) on ultrasound. The clinical appearance of PCOS demonstrates significant heterogeneity. Dyslipidemia is common in PCOS, but variability in study findings means a substantial percentage of women with PCOS may still have normal lipid profiles[4-6]. PCOS symptoms typically start during puberty and worsen with weight gain. Premature pubarche (PP), early development of pubic or axillary hair before age 8 in girls and age 9 in boys, may result from conditions like premature adrenarche and can lead to increased androgens, hyperinsulinemia, and insulin resistance[8,9].

Table 1: Often Occurring PCOS Symptoms [22]

Category	Symptoms/Issues
Metabolic syndrome features	Overweight/obesity Type 2 diabetes
Mental health	Mood disorders (Depression) Nervousness (Anxiety) Compulsive eating (Binge eating)
Elevated male hormone-related skin issues	Excessive hair growth (Hirsutism) Pimples (Acne) Oily skin (Seborrhoea)
Infertility	Trouble conceiving Negative pregnancy outcomes, like higher chances of miscarriage or gestational diabetes
Menstrual irregularities	Infrequent periods (Oligomenorrhea) Absence of periods (Amenorrhea)

Although there are many different clinical presentations of PCOS, anovulation, androgen excess, and insulin resistance are the syndrome's defining characteristics. These factors all lead to hypertension in this population. In seven individuals, a wedge-resection of the ovaries revealed 20–100 follicular cysts per wedge. Comparing polycystic ovaries to controls, histological analysis revealed double the amount of antral follicles, a thicker tunica, and more stroma (Hughesdon, 1982). According to Van der Meer et al. (1998), IVF therapy verified that PCOS patients have a bigger follicular cohort and generate considerably more activated follicles than control individuals. PCOS can cause a variety of complications, such as issues with conception, managing irregular menstruation, and providing relief from hyper-androgenic symptoms including acne, hirsutism, or androgenic alopecia[10].

4. Diagnosis

Through pertinent examinations, differential diagnosis entails ruling out conditions such as hyperprolactinemia, thyroid illness, Cushing's syndrome, and adrenal hyperplasia. Due to the wide range of clinical symptoms and absence of a conclusive diagnostic test, PCOS is difficult to diagnose. The three main components of a diagnosis are polycystic ovarian morphology, irregular menstrual periods, and hyper-androgenism. The Rotterdam criteria are frequently used for adults, requiring the presence of two out of three features while excluding out other diseases. The Polish Diabetes Association's guidelines state that people with PCOS are susceptible to getting diabetes[3-6].

Measuring other androgens, such as androstenedione and dehydroepiandrosterone sulfate (DHEAS), can help assess hyperandrogenism in situations where testosterone levels are normal. DHEAS, a precursor from the adrenal cortex, converts to DHEA, playing roles in neurosteroid function and as a weak adrenal steroid. Up to 20-30% of women with PCOS-like characteristics show excessive adrenal androgen secretion, suggesting a role in PCOS development[8,9].

Finally, it should be noted that diagnosing PCOS requires an in-depth comprehension of its intricate clinical manifestation as well as the application of diagnostic standards specific to the patient's age and reproductive status. Mitigating associated risks, such as the development of diabetes and cardiovascular issues, requires early detection of PCOS and suitable management techniques. Because of this, a multidisciplinary strategy that includes imaging investigations, biochemical examination, and clinical assessment is necessary for precise diagnosis and effective PCOS treatment in a range of age groups[9].

Table 2: PCOS Diagnostic Criteria [12]

In Adults:

1. Classic PCOS (Phenotype 1): - Manifestation of hyperandrogenism, either clinically or biochemically - Presence of irregular ovulation - Identification of polycystic ovaries through ultrasound examination
2. Essential NIH Criteria (Phenotype 2): - Indication of hyperandrogenism, either clinically or biochemically - Manifestation of irregular ovulation
3. Ovulatory PCOS (Phenotype 3): - Display of hyperandrogenism, either clinically or biochemically - Confirmation of polycystic ovaries via ultrasound examination
4. Nonhyperandrogenic PCOS (Phenotype 4): - Evidence of irregular ovulation - Identification of polycystic ovaries through ultrasound examination

For Adolescent:
1. Unexplained combination of: a. Irregular uterine bleeding patterns, deviating from age or gynecologic norms b. Persistent symptoms lasting 1–2 years
2. Indicators of hyperandrogenism: a. Prolonged elevation of testosterone levels beyond adult norms in a reputable laboratory serves as primary evidence b. Clinically significant hirsutism reflects hyperandrogenism

5. Treatment

Managing PCOS in teenagers necessitates a multimodal approach, including lifestyle modifications, medication, and education. The cornerstone consists of lifestyle changes that prioritize psychological support and healthful practices. A small reduction in weight can greatly improve both metabolic and reproductive health, and long-term success in emotional well-being and weight management relies on lifestyle programs that incorporate behavioral strategies. As awareness of antibiotic resistance increases among health-care professionals and the public, research continues to explore its clinical and economic effects[5-6]. We shouldn't expect to find a single long-term effective treatment that would cure polycystic ovarian syndrome because the pathophysiology of this prevalent ailment is not entirely known, despite the fact that at least some cases of the condition have a strong genetic component[10].

5.1 Pharmacological Interventions

To effectively control symptoms, pharmacological interventions are essential. Commonly recommended treatments include oral contraceptives, spironolactone, and metformin. Metformin is particularly helpful for individuals with high insulin levels or glucose intolerance as it decreases testosterone and improves glycemic control. Oral contraceptives, especially combined oral contraceptives (COCs), reduce androgens, increase sex hormone-binding globulin (SHBG), and normalize menstrual cycles. Anti-androgens like flutamide and spironolactone are effective in reducing hirsutism and its bothersome symptoms [18-19]. Overweight, defined as a BMI between 25 and 30 kg/m2, and obesity, defined as a BMI of 30 kg/m2 or above, impact 1.9 billion persons globally, of whom 650 million are obese. Probiotics may be able to assist control body weight since there may be a connection between gut bacteria and obesity, according to emerging research, albeit the findings are yet preliminary[24-30].

Table 3: Medications for Treating PCOS [6].

Drug	Effects	Contrain-dications	Side Effects
Metformin	- Promotes regular menstrual cycles and	- Hyper-sensitivity reactions	- Gastrointestinal discomfort like dyspepsia, diarrhea, nausea,
	- Reduces insulin resistance and improves	- Renal insufficiency or failure	- Unpleasant metallic taste in the mouth
	- Enhances arterial health and lipid profile	- Acute or chronic conditions	- Hepatic and gastrointestinal disturbances, potentially leading
Oral	- Restores menstrual regularity and reduces hyper-androgenism	- History of throm-boembolic events or cardiovascular disorders	- Nausea, vomiting, headache, skin issues like acne and hirsutism
Contracep tives	- Regulates menstrual cycles and mitigates endometrial hyperplasia	- Obesity, pregnancy, or suspected pregnancy	- Weight gain, breast tenderness, mood changes, and vaginal bleeding or spotting
Clomi-fene	- Stimulates ovulation in infertility	- Allergy to clomifene or its	- Headache, tiredness, visual disturbances, nausea and
Eflor-nithine	- Controls excessive facial hair growth	- Hyper-sensitivity to eflornithine	- Skin irritation including burning sensation, dryness, itching,
GnRH analogs	- Suppresses androgen production	- Hyper-sensitivity to the drug or its	- Insomnia, mood swings, reduced libido, vaginal dryness, and
Ketoco-nazole	- Inhibits androgen synthesis	- Severe hepatic disease,	- Nausea, hair loss, dry skin, headache, and potential uterine
Steroids	- Reduces androgen levels and related symptoms	- Contrain-dicated in patients with specific conditions	- Adrenal suppression, infections, psychiatric disturbances, metabolic disorders, osteoporosis, and gastric issues
Spirono-lactone	- Blocks androgens and reduces hirsutism	- Hyper-kalemia, pregnancy, severe renal or hepatic failure	- Breast tenderness, menstrual irregularities, headaches, dizziness, and potential electrolyte imbalances

5.2 Lifestyle Modifications

Effectively managing PCOS involves key lifestyle changes, particularly for overweight adolescents. Regular exercise, with at least 150 minutes per week, improves insulin sensitivity and overall health, with high-intensity intervals and group training enhancing outcomes. Nutrition is crucial, as fat provides 9 kcal/g, while protein and carbohydrates provide 4 kcal/g. Excess fat, easily stored by the body, reduces carbohydrate oxidation and impairs insulin sensitivity, especially with high intake linked to obesity. Unsaturated fats, however, enhance insulin sensitivity, and total fat should be ≤30% of calories, with <10% from saturated

fat, as trans fats increase infertility risk. Cardio-respiratory fitness (VO2max) is essential, with exercise improving VO2max, weight, and waist size. [39-46].

5.3 Individualized Treatment Plans

For symptom relief, adolescents with PCOS or those at risk require individualized treatment plans. It is crucial to provide patients and their families with personalized combination therapies that emphasize joint decision-making for symptom management[8].

5.4 Hormonal and Metabolic Considerations

In women, the most common cause of hyperandrogenism is PCOS, where elevated LH and insulin levels stimulate ovarian theca cells to produce excess androgens. Hyperinsulinemia enhances androgen biosynthesis and reduces SHBG production. Additionally, ACTH-dependent adrenal androgen overproduction further contributes to hyperandrogenemia[20-23]. While HCs effectively manage symptoms, their impact on metabolic parameters such as insulin sensitivity and lipid levels varies. Diet and lifestyle modifications remain crucial for overweight women, with metformin suggested for those with T2DM or intolerance to HCs[25-26].

5.5 Continuity of Care and Psychological Support

To maintain continuous care during the transition to adult healthcare, it is crucial to educate patients on long-term management and select suitable healthcare providers. Addressing psychological issues may involve referrals to counseling, social work, or psychology services. However, the perspectives and experiences of women and healthcare providers in dealing with PCOS-related challenges, such as barriers to effective treatment, remain insufficiently documented[31-35].

5.6 Hirsutism Treatments

Excessive male-pattern hair growth in women, or hirsutism, is usually brought on by hyperandrogenemia; prominent causes include idiopathic hirsutism and polycystic ovarian syndrome[36-38]. Long-term care requires personalized follow-up. Although the exact cause of PCOS pregnancy difficulties is unknown, factors including obesity, insulin resistance, hyperandrogenism, infertility treatments, and placental malfunction may be connected. It is unknown how common spontaneous miscarriages are in women with PCOS[42-49].

6. CONCLUSION

Polycystic Ovary Syndrome (PCOS) presents a multifaceted challenge in diagnosis and management, particularly among adolescents. The intricate interplay of genetic, metabolic, and hormonal factors underscores the complexity of this condition. Diagnosis remains challenging due to overlapping symptoms with normal pubertal changes, necessitating adherence to specific diagnostic criteria and a comprehensive evaluation approach. Treatment strategies must encompass a multimodal approach, including lifestyle modifications, pharmacological interventions, and individualized therapies. Lifestyle changes focusing on diet, exercise, and psychological support are pivotal for long-term management, while medications such as oral contraceptives, metformin, and antiandrogens offer symptom relief. Cosmetic interventions and fertility treatments may also be necessary in certain cases. Lifelong follow-up and multi-disciplinary care are essential to address associated risks and optimize outcomes. By integrating personalized treatment plans that target both metabolic and psychological aspects, healthcare practitioners can effectively manage PCOS in adolescents, thereby improving their quality of life and long-term health outcomes.

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Conflict of Interest

None

Ethical Approval

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