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Polycycstic Ovarian Syndrome (PCOS) in adolescents: a literature review

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ABSTRACT

PCOS is a common endocrine disorder in women of reproductive age, with a prevalence of 5-18%. In adolescents, prevalence rates are lower, with studies indicating rates of 0.8% in the United States and 3% in Iran. The condition is characterized by clinical hyperandrogenism, menstrual irregularities, and polycystic ovarian morphology. The development of PCOS is influenced by multiple factors, including genetic predisposition, insulin resistance, obesity, and hormonal imbalances. Increased luteinizing hormone (LH) and insulin resistance drive excess androgen production in the ovaries. Insulin enhances the effects of LH, contributing to hyperandrogenism and anovulation. Obesity exacerbates symptoms by increasing androgen production and worsening insulin resistance. PCOS is diagnosed based on clinical, biochemical, and ultrasound findings. Hyperandrogenism is evaluated by measuring testosterone levels, and polycystic ovarian morphology is assessed via ultrasound. Imaging studies such as transvaginal ultrasound and MRI may be used when clinical findings are unclear. Management strategies include lifestyle modification, pharmacological therapies, and cosmetic treatments. Lifestyle changes, including diet and exercise, are first-line therapies. Oral contraceptives, antiandrogens, and metformin are commonly used to control symptoms. The goal is to improve quality of life and prevent long-term complications such as metabolic syndrome and type 2 diabetes. PCOS in adolescents requires individualized management to address both immediate symptoms and long-term health risks. Early intervention can improve outcomes and prevent complications associated with the syndrome.

Keywords: polycystic ovarian syndrome, PCOS, adolescents, endocrine.
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INTRODUCTION

Adolescence is a dynamic developmental phase. The World Health Organization (WHO) defines adolescence as the period between the ages of 10 and 19, marked by significant changes in physical growth and development. Polycystic ovary syndrome (PCOS) is a common endocrine disorder primarily found in women of reproductive age.[1,2,3] A meta-analysis reveals that PCOS affects 5-18% of women of reproductive age. In India, the prevalence of PCOS among women aged 15-19 years is 22.6% based on the Rotterdam criteria and 9.8% according to the Androgen Excess and PCOS Society (AES-PCOS) criteria.[3] Population-based studies on the prevalence of PCOS in adolescents are rare, with an estimated prevalence of 0.8% in the United States and 3% in Iran.[4]

Adrenal and Ovarian Steroid Biosynthesis

Initial stimulation of the theca cells by luteinizing hormone (LH) leads to the conversion of cholesterol into androstenedione (Figure 1). Testosterone is synthesized from androstenedione in the theca cells by the enzyme 17β-hydroxysteroid dehydrogenase (17β-HSD) before being converted into dihydrotestosterone. Androstenedione diffuses into granulosa cells, where it is converted into estrone, catalyzed by follicle-stimulating hormone (FSH). The conversion of estrone to estradiol is facilitated by 17β-HSD [5,6]. Concurrently, adrenocorticotropic hormone (ACTH) stimulates steroid biosynthesis in the adrenal cortex (Figure 2).[5,6]

Prior to the formation of progesterone by 3β-hydroxysteroid dehydrogenase (3β-HSD), pregnenolone is synthesized in the zona glomerulosa. Pregnenolone and progesterone are subsequently catalyzed by 17α-hydroxylase into 17-hydroxypregnenolone and 17-hydroxyprogesterone (17-OHP), respectively, in the zona fasciculata. These intermediates are then converted into dehydroepiandrosterone (DHEA) and androstenedione. DHEA may also be converted into androstenedione, which is further transformed into testosterone and estrone. Additionally, androgens are produced in the liver, adipocytes, and skin.[5,6]

The Pathogenesis of PCOS in Adolescents

1. **Potential Factors**
   An in vitro study demonstrates that excess expression of LH receptors and steroidogenic enzymes, such as cytochrome P450c17, 3β-HSD, and 17β-HSD, results in increased production of steroids like 17-OHP and testosterone compared to controls without PCOS. During puberty, the maturation of the

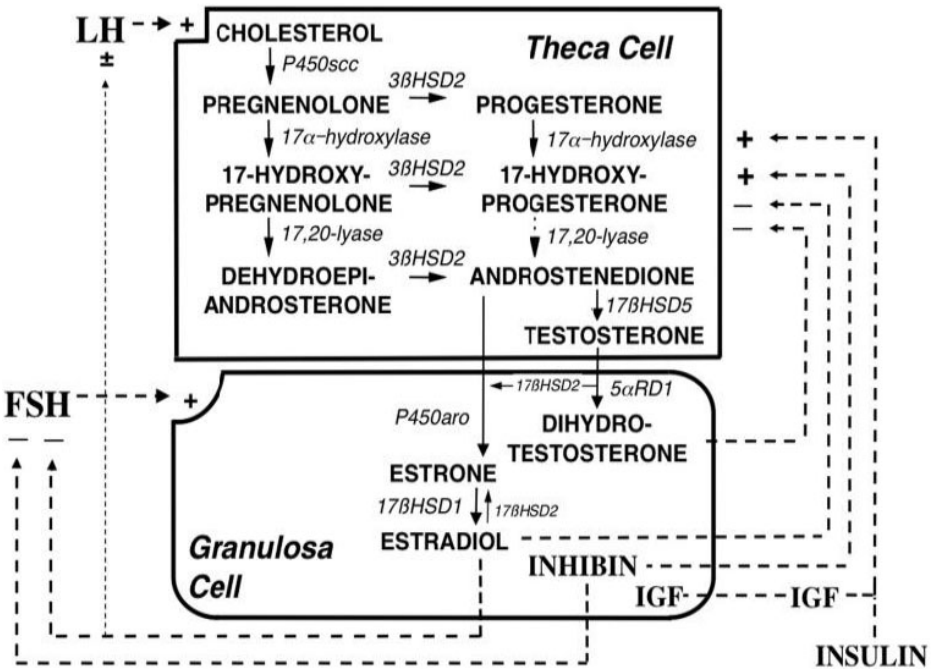

Figure 1. Formation and regulation of steroid biosynthesis in ovarian antral follicles.[6]

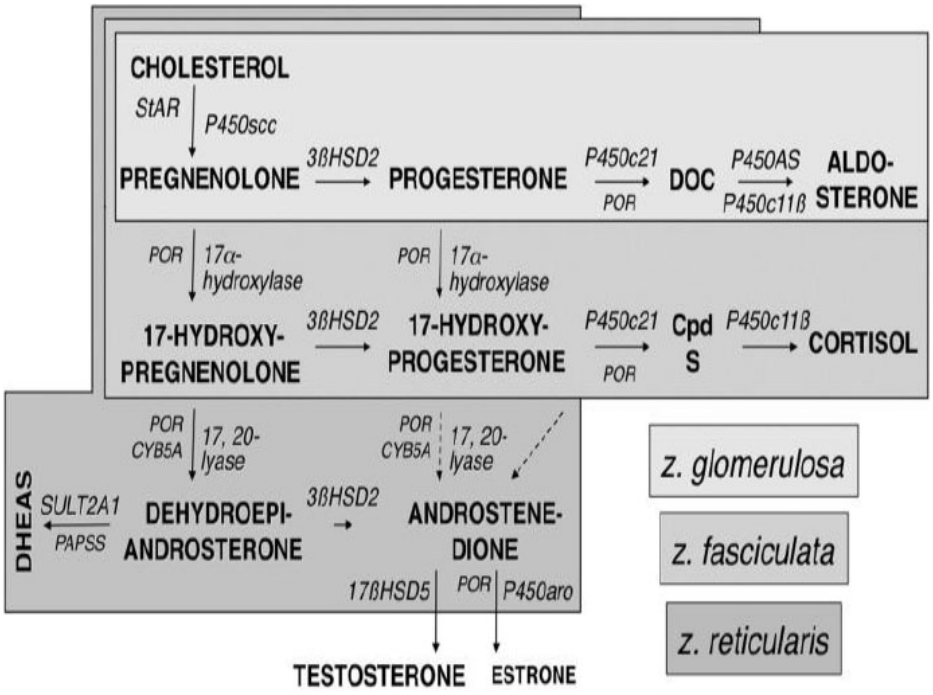

Figure 2. Formation and regulation of steroid biosynthesis in the adrenal cortex.[6]

hypothalamic-pituitary-ovarian axis leads to increased LH levels, which are elevated in women predisposed to PCOS, further increasing androgen production. Adolescents with PCOS exhibit increased frequency and amplitude of gonadotropin-releasing hormone (GnRH) and LH, as well as an elevated LH to FSH ratio.[5,7] Theca cells produce androgens under the influence of LH and other intracrine factors. P450c17 activity is a rate-limiting step in androgen synthesis. Increased expression of P450c17 (CYP17A1) has been observed in theca cells from women with PCOS. Hyperinsulinemia, commonly associated with PCOS, enhances the theca cell response to circulating LH, and ovaries in PCOS exhibit increased enzyme expression from alternative signaling pathways for dihydrotestosterone production.[8,9]

2. **The Role of Insulin and Obesity**
During puberty and adolescence, insulin resistance increases, and serum fasting insulin concentrations rise. Elevated insulin levels decrease the production of sex hormone-binding globulin (SHBG) in the liver, leading to higher free sex steroid levels. Insulin enhances steroidogenesis in theca and granulosa cells through LH stimulation. Despite systemic insulin resistance in PCOS, the ovaries remain sensitive to insulin. Insulin resistance and hyperinsulinemia play a central role in the pathogenesis of PCOS and contribute to anovulation by inhibiting follicular maturation [10]. Obesity exacerbates insulin resistance and hyperandrogenism in PCOS. Excess adipose tissue contributes to increased androgen levels because it contains steroidogenic enzymes that convert androstenedione into testosterone and testosterone into the more potent DHT.[5,6]
3. **Genetic Factors**
Key genes associated with steroidogenesis in PCOS include CYP17A1, CYP19, CYP21, HSD17B5, and HSD17B6. Genes related to insulin biosynthesis and function (INS), insulin receptor (INSR), and insulin receptor substrate (IRS1, IRS2) are also implicated in PCOS. Additionally, genes related to obesity, such as FTO, and cytokines like tumor necrosis factor-α (TNF-α) and interleukins (IL-6, IL-1A, IL-1B) contribute to chronic inflammation in PCOS.[5,12]
Genome-wide association studies (GWAS) in Han Chinese women identified 11 loci strongly associated with PCOS. These findings were validated in Caucasian populations, and the gene *Differentially Expressed in Normal and Neoplastic Development isoform A1* (DDEND1A) was identified as a strong marker of risk.[13,14]
4. **Environmental Factors**
Environmental and lifestyle factors contribute to the pathogenesis of PCOS. Endocrine-disrupting chemicals (EDCs), such as phthalates

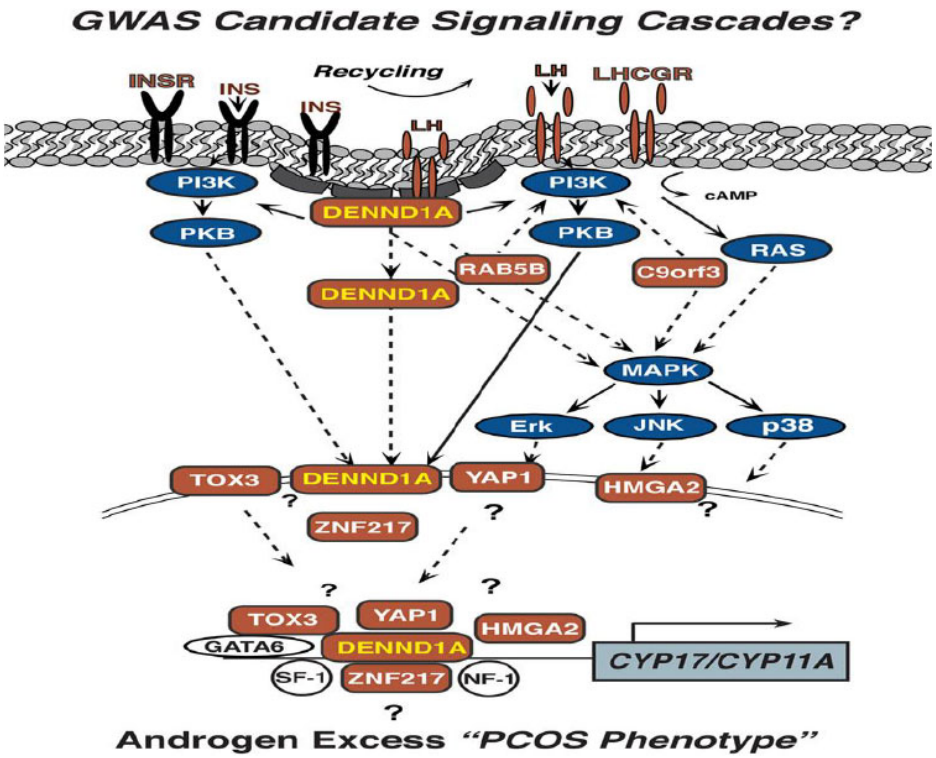

Figure 3. Hypothesis model of the GWAS signaling cascade involved in the pathogenesis of PCOS.[14]

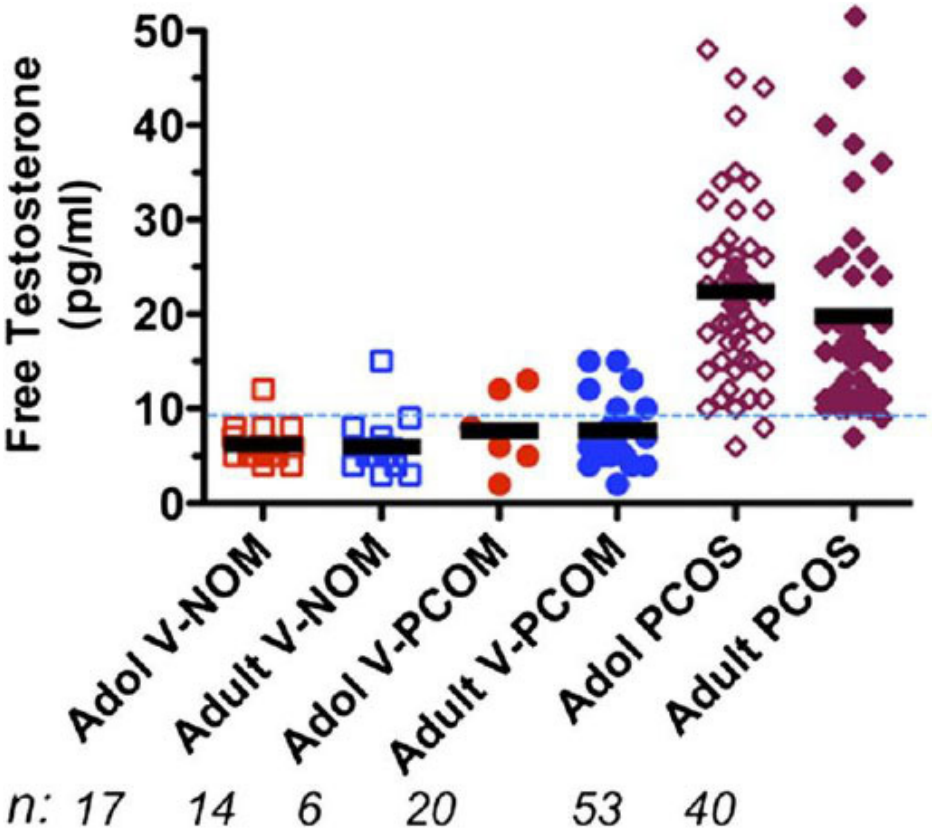

Figure 4. Serum testosterone levels in normal adolescent and adult women after menarche normal ovarian morphology (V-NOM) compared with polycystic ovary morphology (V-PCOM) and PCOS.[16]

and bisphenol A (BPA), are present in food packaging and medical equipment. EDCs can affect hormone biosynthesis and metabolism, leading to various reproductive disorders, including PCOS.[5,15]

Polycystic Ovary Syndrome Diagnosis Criteria in Adolescents

Clinical manifestations of PCOS include clinical hyperandrogenism (hirsutism, acne, and alopecia) and menstrual disorders (primary or secondary amenorrhea, oligomenorrhea, irregular menstrual periods, and heavy menstrual bleeding). Hyperandrogenemia in adolescents is likely a consequence of incomplete maturation of the hypothalamic-pituitary-ovarian axis, as well as prolonged anovulatory cycles typical of pubertal development. These cycles, however, are not an early manifestation of PCOS. Testing of total and/or free testosterone levels is recommended to assess hyperandrogenism. An elevated serum free testosterone level is the most sensitive indicator for hyperandrogenism (Figure 4).[16]

It remains unclear when persistent oligomenorrhea in adolescents becomes a significant clinical finding for PCOS. Insulin resistance and hyperinsulinemia are commonly observed in women with PCOS and may affect the development of the syndrome in some patients. However, the current definition of PCOS in adolescents does not include obesity, insulin resistance, or hyperinsulinemia as diagnostic criteria.[2,17-19]

The Endocrine Society clinical guidelines recommend diagnosing PCOS in adolescents using criteria for hyperandrogenism and persistent anovulatory menstrual disorders that cannot be explained by other causes. The evidence supporting this recommendation is limited, prompting The Pediatric Endocrine Society to invite representatives from pediatric, adult, and reproductive endocrinologists, adolescent medicine specialists, and the subspecialty of adolescent gynecology to discuss the appropriate criteria for diagnosing PCOS in adolescents.[16]

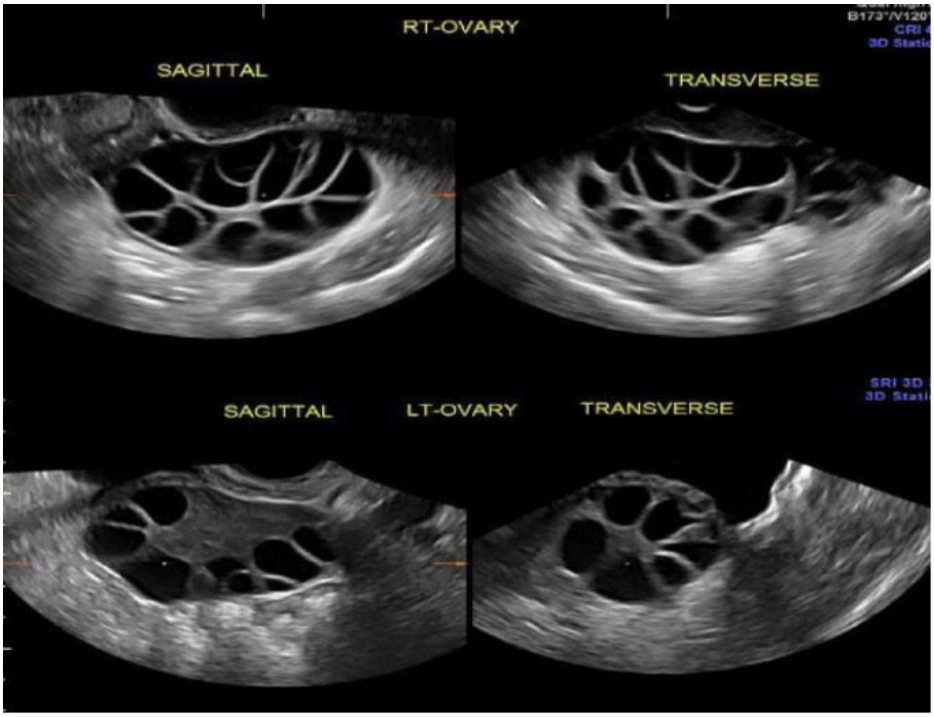

Figure 5. Display of TVS examination on PCOS.[20]

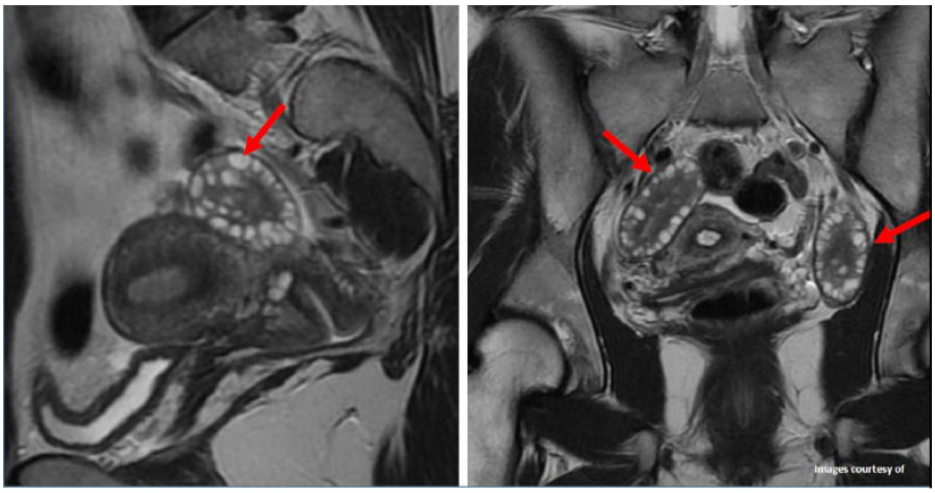

Figure 6. Display of MRI examination on PCOS.[21]

Imaging studies can be used to confirm the diagnosis of PCOS when clinical and laboratory evaluations are unclear (Figure 5). Transvaginal ultrasound is the preferred modality for this purpose. In cases where clinical and laboratory findings are uncertain, MRI can serve as an accurate diagnostic imaging modality (Figure 6).[20,21]

Management of Polycystic Ovarian Syndrome in Adolescents

Management of PCOS in adolescents should be individualized to meet each patient's needs. The goal of treatment is to improve quality of life, achieve long-term health outcomes, and manage the side effects of treatment. While there is no specific treatment targeting the underlying causes and pathophysiology of PCOS, therapy generally consists of two components: first, controlling the symptoms of hyperandrogenism (hirsutism, acne, irregular menstrual cycles, or infertility); and second, preventing long-term morbidity associated with PCOS (e.g., metabolic syndrome, type 2 diabetes, emotional health, and self-confidence). Effective communication with adolescents regarding their concerns is crucial for engagement and adherence to the treatment plan. Available therapeutic options include lifestyle interventions, local cosmetic therapy, pharmacological therapy, and combined therapies.[5,13,17,22]

Lifestyle modification is considered the first-line therapy for all PCOS patients. A small randomized clinical trial in adolescents showed that a healthy lifestyle (dietary restrictions with intense exercise) increased the number of menstrual cycles, decreased hirsutism scores, and reduced testosterone levels by increasing SHBG. One study comparing exercise to a low-calorie diet found that the exercise group had a higher ovulation rate (65% vs 25%) and pregnancy rate (6.2% vs 1.7%). Both groups showed improvements in body weight, androgen levels, fasting glucose, and insulin resistance. The diet group showed a greater reduction in body weight (10% vs 5%) and a greater decrease in androgen levels, whereas the exercise group showed a greater increase in SHBG levels, reduced testosterone, free androgen index, and insulin resistance compared to the diet group.[23,24]

Cosmetic hair removal methods for managing hirsutism include bleaching, chemical epilation, plucking, waxing, shaving, electrolysis, and laser hair removal. Electrolysis can result in permanent hair removal, although its efficacy and safety have not been consistently supported by randomized controlled trials (RCTs).[17]

Combined oral contraceptives (COCs) containing estrogen (ethinylestradiol) and progestin (progesterone) are considered first-line treatment for adolescents with PCOS to reduce hyperandrogenism and/or regulate menstrual cycles. The estrogen component increases SHBG levels, which reduces the bioavailability of testosterone by binding to free steroids, ultimately alleviating symptoms of androgen excess. Progestins lower LH levels, reducing ovarian androgen production. COCs also provide menstrual regulation and endometrial protection.[5,17,25,26]

A meta-analysis on metformin use, with or without lifestyle changes, in PCOS patients in 2014 demonstrated beneficial effects on BMI and menstrual cycles. Observational studies and six clinical trials found short-term benefits of metformin in adolescents with PCOS,

particularly those who are overweight or obese. A recent meta-analysis comparing metformin and COCs, including four RCTs with 170 adolescents, showed that both treatments provided similar benefits for hirsutism, triglyceride levels, and HDL cholesterol.[17,25,27,28]

Antiandrogen therapies for PCOS include androgen receptor blockers (spironolactone and flutamide), third-generation progestins (cyproterone acetate), and 5α-reductase inhibitors (finasteride). However, RCTs directly comparing antiandrogens in adolescents with PCOS are lacking. Spironolactone is commonly used due to its availability and safety, with an initial dose of 25 mg/day gradually increased to a maximum of 200 mg/day. Initial treatment with spironolactone may be associated with transient irregular menstruation, spotting, breast pain, and sometimes fatigue or orthostasis due to decreased blood volume. Treatment with antiandrogens significantly reduces hirsutism compared to placebo, and when combined with metformin, it leads to better outcomes in normalizing menstrual cycles and improving endocrine-metabolic variables.[17,29]

CONCLUSION

Polycystic ovary syndrome (PCOS) is a long-recognized, complex familial disorder. The pathogenesis of PCOS involves multiple biological systems, including changes in steroidogenesis, ovarian folliculogenesis, neuroendocrine function, metabolism, insulin secretion and sensitivity, adipose cell function, inflammatory factors, and sympathetic nerve function. PCOS is characterized by ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology based on ultrasonography. In adolescents, clinical manifestations of PCOS include hyperandrogenism (hirsutism, acne, alopecia) and menstrual disorders (primary or secondary amenorrhea, oligomenorrhea, irregular menstrual periods, and heavy menstrual bleeding). Testing of total and/or free testosterone levels is recommended to assess hyperandrogenism. The upper limit for total testosterone is generally considered to be 55 ng/dL, while for free testosterone, it is 9 pg/dL. Polycystic ovary morphology in adult women, according to consensus criteria, is defined as an ovary with a volume >10.0 mL or a small antral follicle 2-9 mm in diameter, with a count of ≥12 follicles. The same criteria are found in one-third to one-half of normal adolescents. The primary goal of treatment is to improve the quality of life and obtain long-term health outcomes while balancing treatment side effects. Treatment involves two components: controlling hyperandrogenism symptoms (hirsutism, acne, irregular menstrual cycles, or infertility) and preventing long-term morbidity (metabolic syndrome, type 2 diabetes, emotional health, and self-confidence).

ETHICAL CONSIDERATIONS

Not Applicable.

DECLARATION OF CONFLICTING INTERESTS

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AUTHOR CONTRIBUTIONS

All authors contributed to data gathering, analysis, drafting, and revising and approving the article regarding this research to be published.

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