POLYCYSTIC OVARY SYNDROME: DIVERSE CLINICAL PRESENTATIONS ACROSS ADOLESCENCE, REPRODUCTIVE AGE, AND MENOPAUSE

Plamena Kabakchieva¹ https://orcid.org/0000-0003-3577-0577

¹Clinic of Internal Medicine, Naval Hospital Varna, Military Medical Academy, Bulgaria

Received: May 5, 2024
Accepted: June 19, 2024

Corresponding author: Plamena Kabakchieva E-mail: plamenakabakchieva@yahoo.com
Twitter handle: @PKabakchieva

Abstract
Polycystic Ovary Syndrome (PCOS) is a multifaceted endocrine disorder affecting women across various life stages, presenting a wide array of symptoms that differ markedly during adolescence, reproductive age, and menopause. In adolescence, the overlap of PCOS symptoms with normal pubertal changes complicates diagnosis, with common presentations including menstrual irregularities, acne, and hirsutism. During the reproductive years, PCOS is often associated with infertility, menstrual dysfunction, and metabolic complications such as insulin resistance and type 2 diabetes. In menopausal women, reproductive symptoms diminish, but the risk of cardiovascular disease, persistent hyperandrogenism, and metabolic syndrome becomes more pronounced. This review aims to define the distinct clinical presentations of PCOS across these life stages, highlighting the diagnostic and management challenges inherent to its heterogeneous nature. By understanding the age-specific manifestations and complications of PCOS, healthcare providers can develop more effective, individualized therapeutic strategies, ultimately improving patient outcomes and quality of life.

Keywords: polycystic ovary syndrome; clinical presentation; adolescence; reproductive age; menopause

How to cite: Kabakchieva P. Polycystic Ovary Syndrome: Diverse Clinical Presentations Across Adolescence, Reproductive Age, and Menopause. Anti Aging East Eur 2024;3(2): 78-86  https://doi.org/10.56543/aaeeu.2024.3.2.04

Key Messages for Research and Practice

• PCOS symptoms vary widely across life stages, complicating diagnosis, especially during adolescence when symptoms overlap with normal pubertal changes.

• Individualized treatment approaches are essential for addressing the diverse symptoms and complications of PCOS during reproductive years and menopause.

• Understanding age-specific PCOS manifestations enables healthcare providers to develop effective, personalized therapies that enhance patient outcomes and quality of life.
Introduction

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous endocrine-metabolic disorder characterized by a range of symptoms and signs including androgen excess (manifesting as hirsutism and/or hyperandrogenemia), ovulatory dysfunction, and polycystic ovarian morphology. Additionally, PCOS is associated with significant metabolic disturbances, such as an increased risk of insulin resistance, prediabetes, type 2 diabetes, metabolic syndrome, and cardiovascular diseases. Psychological issues, including heightened anxiety and depression, also contribute to an impaired quality of life among affected individuals [1].

The condition affects approximately 5-10% of women of reproductive age; however, its true prevalence may be higher due to the variability in diagnostic criteria and the diverse clinical presentations of PCOS [2]. This variability makes PCOS one of the most common endocrinopathies worldwide, with estimates suggesting it affects between 1 in 10 and 1 in 7 women of reproductive age. PCOS is a leading cause of infertility, responsible for up to 80% of anovulatory infertility cases [3]. Despite its prevalence and impact, up to 70% of women with PCOS remain undiagnosed, highlighting a significant gap in awareness and diagnosis that necessitates improved clinical recognition and management strategies [4,5].

The syndrome was first described by two gynecologists from Chicago, Irving Stein and Michael Leventhal. In their publication in 1935 titled «Amenorrhea associated with bilateral polycystic ovaries,» they detailed their clinical observations of seven women who presented with menstrual disturbances (amenorrhea), infertility, and hyperandrogenism, all associated with enlarged cystic ovaries, as identified by transabdominal pneumography [6]. The initial report highlighted the heterogeneous clinical presentation of PCOS. Among the seven women, three were obese, four exhibited hirsutisms (with one also being obese), and one woman was thin, suffering from amenorrhea, acne, and bilateral lower abdominal pain for a year. This early documentation underscored the variability in symptoms and physical manifestations, a hallmark of PCOS that continues to challenge diagnosis and treatment.

PCOS was historically regarded as a condition predominantly affecting women of reproductive age. However, contemporary medical guidelines recognize PCOS as a lifelong disorder that manifests differently across various stages of a woman’s life [7]. Consequently, the diagnosis of PCOS should be considered during adolescence, reproductive age, and menopause, with each stage presenting unique clinical characteristics and diagnostic challenges.

This review aims to provide a detailed examination of the clinical presentations and diagnostic processes of PCOS in each of these three life stages. By highlighting the distinct features and challenges at each stage, we aim to enhance the understanding of PCOS as a lifelong condition, thereby improving diagnostic accuracy and patient management across the lifespan.

Search strategy

We employed a methodical approach inspired by the recommendations of Gasparyan et al. [8]. To ensure comprehensive coverage, a systematic search was conducted in the PubMed (MedLine) and Scopus databases on June 1, 2024, using the keywords «PCOS,» «adolescence,» «reproductive age,» and «menopause.» Following rigorous criteria to exclude duplicates and irrelevant articles, we concentrated solely on original research papers. This careful process resulted in a curated selection of studies that were included in sections exploring the diverse clinical presentations of PCOS at different life stages. To provide a comprehensive background, we also integrated a variety of review articles, society guidelines, and expert recommendations. These were sourced from multiple database searches and enriched by the authors’ expertise in the field.

PCOS diagnosis and phenotype groups

PCOS is a complex endocrine disorder characterized by a combination of three primary diagnostic features: hyperandrogenism (which can be clinical, such as hirsutism, or biochemical, such as elevated androgen levels), ovulatory dysfunction (manifesting as irregular or absent menstrual cycles), and polycystic ovarian morphology (PCOM) (typically identified via ultrasound as enlarged ovaries with multiple cysts). According to the widely accepted Rotterdam criteria [9], a diagnosis of PCOS is confirmed when at least two of these three features are present. This diagnostic framework allows for the identification of four distinct phenotypic groups of PCOS:

- Phenotype A (Complete PCOS): Characterized by the presence of hyperandrogenism, ovulatory dysfunction, and polycystic ovaries.
- Phenotype B (Non-polycystic ovary PCOS): Involves hyperandrogenism and ovulatory dysfunction but lacks polycystic ovarian morphology.
• Phenotype C (Ovulatory PCOS): Includes hyperandrogenism and polycystic ovarian morphology but regular ovulatory cycles.

• Phenotype D (Non-hyperandrogenic PCOS): Defined by ovulatory dysfunction and polycystic ovarian morphology without hyperandrogenism.

Phenotype A and B are often referred to as the classical phenotypes of PCOS. Both typically exhibit the most pronounced clinical and metabolic manifestations, including severe insulin resistance. Phenotype C generally has a milder clinical picture concerning metabolic manifestations. However, individuals with Phenotype C are at a higher risk for ovarian hyperstimulation syndrome, with metabolic issues being less severe compared to Phenotype A and B. According to the AE-PCOS Society Task Force [10], the presence of hyperandrogenism is the feature most strongly associated with long-term comorbidities, such as type 2 diabetes and other metabolic diseases.

Due to the three phenotypes A, B and C are defined as clinically significant, while the phenotype D (non-hyperandrogenic PCOS), in which hyperandrogenism is absent, has the mildest clinical manifestation on of insulin resistance and metabolic manifestations (Figure 1).

To summarize, the diagnosis of PCOS is made on the basis of evaluation of hyperandrogenic status, ovulatory function and menstrual history, ultrasound determination of ovarian morphology while excluding diseases and conditions that may cause them such as pregnancy, thyroid disease, hyperprolactinemia, premature ovarian failure, hypothalamic amenorrhea, congenital adrenal hyperplasia, androgen-producing tumor, Cushing’s syndrome or disease. After diagnosis of PCOS is confirmed, the phenotype (A, B, C, or D) should be determined because as already noted each phenotype is associated with a different risk for metabolic and other diseases.

Figure 1. Illustration of the clinical presentation of PCOS phenotypes: Classic PCOS phenotype (phenotype A and B) combining hyperandrogenism (hirsutism, acne, female pattern hair loss), oligo-anovulation (menstrual disorders, infertility, endometrial hyperplasia) with/without polycystic ovary morphology (PCOM) with most severe clinical manifestation of the metabolic manifestations marked (+++). Ovulatory PCOS phenotype (phenotype C), presenting hyperandrogenism and PCOM and a milder degree of clinical presentation of the metabolic manifestations marked with (++). Non-hyperandrogenic PCOS phenotype (phenotype D) combining oligo-anovulation and PCOM and mildest presentation of metabolic manifestations marked (+/-). Adaptation from [11].
Diagnostic characteristics

Hyperandrogenism

Hirsutism is the most common clinical sign of hyperandrogenism [12], with a reported incidence of about 75–80% in different studies [13, 14]. According to the guidelines, hirsutism is highly predictive of the presence of biochemical hyperandrogenism [15], making it a leading clinical indicator of androgen excess.

Hirsutism is defined as the appearance of terminal hairs (long > 5 mm, pigmented, thickened hairs) in androgen-dependent areas of the woman. They differ from the vellus hairs, which are thin, soft, unpigmented and are mostly in areas whose growth is not controlled by androgens.

Usually, the appearance of hirsutism occurs after menarche. It develops gradually and its intensity increases with increasing body weight, while in neoplastic virilizing tumors there is a rapid appearance of severe hirsutism, often associated with clitoromegaly and oligomenorrhea [15].

Clinical evaluation of the degree of hirsutism is performed using the modified Ferriman-Gallwey scale (mFG score) [16], which assesses the degree of hair growth in 9 androgen-dependent areas of the body (upper lip, chin and neck, chest [excluding nipples], upper and lower back, upper and lower abdomen [above and below the belly button], arm, inner thighs) on a scale of 1 (minimum presence of terminal hair) to 4 (presence of terminal hair similar to those of a well-haired man). The absence of terminal hairs in the examined area is marked with 0.

According to the recommendations for the diagnosis and treatment of PCOS, the presence of hirsutism is accepted when there is a mFG score ≥ 4-6 [5, 7]. Further attention is being paid to ethnic-related variations in hirsutism, with a common more severe pattern of androgen-dependent hair among women from the Middle East, Spain and the Mediterranean [5].

Acne is an inflammatory condition of the hair follicle and the adjacent sebaceous and apocrine glands (pilo-sebaceous unit). It is characterized by increased sebum production, impaired differentiation of the follicular epithelium, increased keratinization leading to blockage of the pilo-sebaceous unit by desquamated epithelial cells, growth and development of microbes (e.g. Propionibacterium acnes) and, as a final effect, the appearance of local inflammation [17].

Acne occurs in 15–25% of women with the syndrome, and this incidence varies by ethnicity [18]. Due to the fact that it is a common dermatological problem among adolescents, acne is not recommended to be used as a diagnostic marker of hyperandrogenism at this age [19]. Severe adolescent acne, acne persisting after puberty, or new onset after 20-30 years of age, could be considered a clinical sign of hyperandrogenism [7, 15].

However, according to recommendations, the isolated appearance of acne, without the presence of hirsutism, has a low predictive role in the diagnosis of hyperandrogenism of PCOS [7]. Additionally, there is a lack of an accurate acne assessment tool [7, 20]. Given its lower frequency of occurrence and specificity, acne has a rather secondary role in the diagnosis of clinical hyperandrogenism.

Female pattern hair loss (FPHL). Recently, the term «androgenic alopecia» has been replaced by FPHL. This change in terminology is intended to distinguish between the different characteristics of the condition in women and men, and indicates the lack of clear hormonal contributions in many cases of FPHL presentation.

In fact, the reasons for its appearance are not fully understood. Multiple mechanisms have been proposed to be associated with visible thinning of scalp hair resulting from a progressive reduction in the ratio of terminal to vellus hairs, a process termed follicular miniaturization [21].

The normal hair cycle includes three phases: growth (anagen), transitional (catagen) and resting phase (telogen), in which the old hair follicles are already fully prepared to fall out and be replaced by new ones.

It is known that androgen overexposure results in a shortening of the anagen phase due to the direct effects of dihydrotestosterone (DHT), which is more potent androgen than testosterone binding to androgen receptor in hair follicles [22]. Presentation of hairs of different lengths and diameters are a hallmark of FPHL and androgenic alopecia [22, 23]. Interestingly, the density of follicles per unit area remains unchanged [24]. The pattern of hair thinning typically spares the occiput, reflecting regional differences in follicle sensitivity to androgens. Most women with FPHL do not exhibit other signs or symptoms of hyperandrogenism and have normal androgen levels, indicating that androgens are not the sole causative factor. Moreover, studies show that the incidence of FPHL increases with age, predominantly among postmenopausal women, which suggests that estrogens play a role as protectors of hair loss.
Given the complex etiology of FPHL, its isolated manifestation should play a limited role in diagnosing clinical hyperandrogenism among women with PCOS. There are two recommended scales for its evaluation: the Olsen scale (the «Christmas Tree» model) [25] and the Ludwig scale [26].

Biochemical hyperandrogenism

Measurement of total testosterone is a screening test for evidence of hyperandrogenemia in patients with hirsutism [18]. However, 33-50% of women with hirsutism can be found to have normal testosterone levels. This is because total testosterone levels are affected by sex-hormone binding globulin (SHBG) levels, which bound 65% of testosterone. Therefore, women with low SHBG levels may be found to have normal total testosterone levels and this may be a reason to miss hyperandrogenemia that actually exists [27]. In view of this, testing of free testosterone or calculation of free androgen index (FAI), as its alternative, is recommended [7].

Determination of dehydroepiandrosterone sulfate (DHEAS) and androstenedione levels are of additional diagnostic value in cases of normal total and/or free testosterone (FAI) [7].

Hormonal tests for androgens should be performed in the morning hours, during the early follicular phase (between the 3rd and 5th days of the menstrual cycle) of a spontaneous menstrual cycle or progestogen-induced menstrual bleeding and in the absence of hormonal contraception > 3 months [28]. Cutoffs vary by assay and method, but total testosterone levels > 1.4 nmol/L and/or FAI > 3.5 points among adolescents and total testosterone > 1.6 nmol/L and/or FAI > 5 among mature women confirm the presence of biochemical hyperandrogenism [29, 30].

Ovulatory dysfunction

Menstrual disturbances in PCOS result from an imbalance involving the inhibitory effect of androgens, the stimulatory effect of insulin, and acyclic hyperestrogenemia on the endometrium [31]. These disturbances most commonly present as oligo-/amenorrhea; however, dysfunctional uterine bleeding can also occur due to hyperestrogenemia. The International Recommendations for the Evaluation and Treatment of PCOS consider age when defining irregular menstrual cycles:

- Menstrual cycle shorter than 21 days or longer than 35 days, or fewer than 8 menstrual cycles per year, in the period from 3 years after menarche to menopause.
- Menstrual cycle longer than 90 days for each cycle in girls up to 1 year after menarche.
- Primary amenorrhea by age 15 or 3 years after thelarche [7].

Polycystic ovary morphology (PCOM)

The polycystic ovary is characterized by increased size, an elevated number of growing follicles, and increased stromal volume. Utilizing a transvaginal ultrasound method with a transducer frequency of at least 8 MHz, the presence of PCOM is identified by the presence of multiple follicles (sized between 2-9 mm) in at least one ovary, meeting criteria such as follicle number per ovary (FNPO) ≥ 20 or follicle number per cross-section (FNPS) ≥ 10, and/or ovarian volume ≥ 10 ml. In cases where older ultrasound methods or technical limitations lead to lower-quality images, the parameters for assessing PCOM should adhere to FNPS ≥ 10 and/or ovarian volume ≥ 10 ml.

It is sufficient for diagnostic purposes if these changes affect only one ovary, confirmed by ultrasound findings that demonstrate the absence of a corpus luteum, cysts, or dominant follicles in that specific ovary. [7].

Importantly, PCOM should not be used as a diagnostic criterion in adolescents until at least 8 years after menarche [7]. This recommendation is based on two main considerations. First, in adolescents, ovarian ultrasound examinations are typically performed transabdominally rather than transvaginal, which can compromise the accuracy of the imaging. Second, the presence of PCOM is a common and often transient finding in healthy adolescents, making it an unreliable indicator of PCOS in this age group [33-35]. Additionally, there is significant overlap in the presentation of PCOS in healthy and adolescent girls with PCOS, further complicating the use of PCOM as a diagnostic tool during this stage of development [33-37].

Clinical manifestation and diagnostic algorithm in different ages

After reviewing the diagnostic algorithm for PCOS and its three diagnostic characteristics, we will examine their manifestations in the three age groups: adolescence, reproductive age, and menopause (Figure 2).
while minimizing the risk of overdiagnosis and overtreatment. Lifestyle modifications, including diet and exercise, are the first-line treatments to manage symptoms and reduce the risk of long-term complications. Hormonal treatments, such as combined oral contraceptives, are commonly used to regulate menstrual cycles and lower androgen levels. Metformin may be considered for adolescents with insulin resistance at the maximum recommended dose of 2 grams. Additionally, anti-obesity drugs may be used for weight control, which can help regulate menstruation and reduce hyperandrogenism [7].

2. Reproductive Age

Women of reproductive age with PCOS often present with menstrual irregularities, infertility, and hyperandrogenism. Metabolic issues, such as insulin resistance, type 2 diabetes, and obesity, are also prevalent. The impact of PCOS on fertility is significant, often leading to anovulation and difficulty in conceiving.

The Rotterdam criteria are widely used to diagnose PCOS in reproductive-aged women [9]. At this age, AMH levels may serve as an alternative to ovarian ultrasound for identifying PCOM [7]. It is essential to rule out other causes of hyperandrogenism and menstrual irregularities before confirming a PCOS diagnosis.

To prevent long-term complications such as metabolic syndrome, gestational diabetes, and other pregnancy-related issues, it is essential to assess several health parameters in all women with PCOS, regardless of their body mass index (BMI), at the time of diagnosis. These assessments should include lipid profile (total cholesterol, low-density
lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides), oral glucose tolerance test (OGTT), HbA1c levels, and blood pressure [7].

Additionally, premenopausal women with PCOS are at an increased risk of endometrial hyperplasia and endometrial cancer. Risk factors for these conditions include prolonged amenorrhea, overweight/obesity, type 2 diabetes, and persistent endometrial thickening. To mitigate these risks, the following preventive measures are recommended: weight control, menstrual regulation, and regular progesterone therapy [7].

Management strategies during reproductive age are tailored to the patient’s symptoms and fertility desires. For those not seeking pregnancy, combined oral contraceptives with low-dosed estrogen component are preferred to manage menstrual irregularities and hyperandrogenism. Anti-androgen preparations remain as a second line for the treatment of hirsutism in case of failure of 6 months of hormonal contraceptives treatment, contraindication to their use or intolerance to them. The need for good contraception during monotherapy with them is emphasized.

Lifestyle interventions remain a cornerstone of management, particularly for addressing metabolic concerns. Metformin is a potential monotherapy for mature women with a BMI ≥ 25 kg/m² and insulin resistance, with the recommended maximum dose being 2.5 grams. Its effect is limited in women with a BMI < 25 kg/m².

Among the anti-obesity medications, glucagon-like peptide-1 (GLP-1) receptor agonists such as liraglutide and semaglutide, as well as orlistat, are listed as possible therapies for combating excess weight. It is crucial to emphasize the need for effective contraception during the use of GLP-1 agonists.

For women seeking to conceive, ovulation induction agents, such as letrozole or clomiphene citrate, are commonly prescribed. The recommendation for letrozole as first-line therapy for ovulation induction remains. Second line can be: metformin monotherapy, clomiphene citrate monotherapy, or a combination of both (metformin + clomiphene citrate), falling into the category of «low efficacy», or with gonadotropins as a more effective therapy. Laparoscopic surgery is a possible alternative to second-line therapy for ovulation induction.

In-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) represent third-line infertility treatments, each with specific protocols designed to minimize the risk of ovarian hyperstimulation syndrome. Another potential therapeutic option is in vitro maturation, particularly suitable for women at increased risk of ovarian hyperstimulation syndrome, despite statistically lowers success rates [7].

3. Menopause

The clinical presentation of PCOS in menopausal women is less well defined, as many reproductive symptoms, such as menstrual irregularities, resolve. However, hirsutism and biochemical hyperandrogenism often persist during the peri- and postmenopausal periods [38]. In menopausal women with PCOS, levels of androgens, including total testosterone, FAI, and androstenedione, are elevated compared to controls. Possible reasons for this include increased adrenal androgen production [39], enhanced ovarian production of 17-OH-progesterone or androstenedione [39], or stable ovarian and adrenal androgen production even after menopause [40].

Contrary to common expectations, postmenopausal women with PCOS have a risk of cardiovascular disease, type 2 diabetes, and metabolic syndrome comparable to that of the control group. Recent meta-analyses suggest that obesity, particularly visceral adiposity, plays a central role in worsening the metabolic profile among women with PCOS.

There is no established algorithm for diagnosing PCOS in menopausal women. The diagnosis can be inferred based on a retrospective history that includes the presence of hirsutism, biochemical evidence of hyperandrogenism, oligo-amenorrhea, and infertility without male factor involvement. The combination of these historical factors, along with current evidence of central obesity, insulin resistance, or biochemical hyperandrogenism, suggests a diagnosis of PCOS [41-43].

Management should focus on mitigating the increased cardiovascular and metabolic risks associated with the syndrome, with a particular emphasis on weight reduction. Although there is no specific treatment for PCOS in menopausal women, several medications can be considered to address these issues. GLP-1 agonists or orlistat can be used to control body weight, metformin is effective in correcting insulin resistance, statins are prescribed to manage dyslipidemia, and antihypertensive medications are utilized to control arterial hypertension. Regular monitoring and management of metabolic health, including glucose
tolerance, blood pressure control and lipid profiles, are essential to prevent cardiovascular disease and mortality.

Conclusion

PCOS is the most common endocrine disorder affecting women across all life stages—adolescence, reproductive age, and menopause—considering the syndrome as a lifelong condition. It presents with diverse clinical manifestations that vary significantly across these different stages of life. Recognizing and understanding these variations are crucial for effective diagnosis and management. Tailoring treatment strategies to the individual’s age and specific symptomatology can significantly improve quality of life and mitigate long-term health risks.

REFERENCES


