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Update on diagnosis and management of polycystic ovarian syndrome

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By:
Hussain Ammar Hashem
Zainab Abdulkader Ahmed
Dania Hatem Obaid

Supervised by:
Asst.Dr.Fatma Adnan Ali

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وقل رب زدني علما

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In the name of Allah, the most merciful, the most compassionate.

We would like to thank God for his mercy and grace, and we hope that God will accept this work with good acceptance

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Hussain Ammar Hashem

Zainab Abdulkader Ahmed

Dania Hatem Obaid

Dedication

To those who lit the first light in my life…..

To those who exerted the effort of years in generosity, and make from days stairs for me to rise…..

my mother and my father.

To everyone whom taught us anything ever, our teachers.....

Summary

The most prevalent and still incurable endocrine condition in women of reproductive age is polycystic ovary syndrome. With the right medicine and lifestyle changes, the symptoms can be successfully treated. Although it is common, little is understood about its pathogenesis. The most recent diagnostic features and parameters that have been advised based on data from reliable sources and various guidelines are examined in this review article. Focus has been placed specifically on the ambiguity and lack of evidence when assessing adolescent women.

This article also discusses current treatment methods and potential areas for progress in the near future. It describes the various clinical trials that have been carried out over the years that have examined various therapies as prospective treatments. Future research could shed some light on this problem with female reproductive health and provide direction toward a long-term solution, ranging from conventional medicines like metformin to recently discovered alternatives based on vitamin D and gut bacteria.

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List of Abbreviations

Abbrev.	Meaning
11-HSD	11-hydroxysteroid dehydrogenase
AGEs	advanced glycation end products
CRP	C-reactive protein
EDC	endocrine-disrupting chemical
EPHX1	epoxide hydrolase 1
GPCR30	G-protein coupled receptor
HA	hyperandrogenism
HPA	hypothalamic-pituitary-adrenal
IRS	insulin receptor substrate
LHCGR	LH/choriogonadotropin receptor
NEFAs	non-esterified fatty acids
PBA	bisphenol A
PCOM	polycystic ovarian morphology
PCOS	polycystic ovarian syndrome
PPAR-γ	peroxisome proliferator-activated receptor gamma
PVC	polyvinyl chloride
SFAs	saturated fatty acids
USEPA	United States Environmental Protection Agency
VTE	venous thromboembolism

1.Introduction:

A common metabolic and endocrine condition affecting women of reproductive age is polycystic ovarian syndrome (PCOS). Three key characteristics of the illness—irregular menstruation, hyperandrogenism, and polycystic ovarian morphology—are present in varying degrees (PCOM) **(1)**.

According on the many definitions employed, the prevalence of PCOS is estimated to be between 5% and 20%. Despite numerous improvements and modifications made to the diagnostic standards and interpretation of the pathophysiology of the problem, PCOS is still a disorder that lacks standardized diagnostic and therapeutic standards.

The disease's complex consequences last throughout a woman's lifespan, starting at conception and continuing for years after menopause. The majority of PCOS-related studies were conducted with the goal of creating a rapid and accurate diagnosis, especially for adolescents, effective treatment, management of PCOS-related comorbidities that have a serious impact on quality of life, and a uniform protocol that can be used by healthcare professionals. The diagnostic techniques and other screening protocols discussed in this review were based on the most recent international evidence-based recommendations for PCOS.

The knowledge that a certain proportion of women are still receiving incorrect diagnoses or going untreated as a result of ignorance and misunderstanding provided the motivation to work with PCOS**(2)**.

1.1 Etiology and Risk factors associated with PCOS:

1.1.1. External Factors:

1.1.1.1.Mechanism of Epigenetics:

Epigenetic refers to inheritable alterations in genome and gene expression without any changes in DNA sequence **(2)**. These changes involve adding or omitting chemical components on DNA or histone. Increased LH activity is a seen phenomenon in PCOS women. It may relate to the problems in follicle development and HA, which are common among PCOS patients. LH/choriogonadotropin receptor (LHCGR) is responsible for the steroidogenesis process in theca cells .This receptor hypomethylation leads to higher gene expression and sensitivity to LH **(3)**.

A study on PCOS patients approved that hypomethylated sites are related to overexpression of LHCGR on theca cells surface . In addition, epoxide hydrolase 1 (EPHX1) is an active enzyme in degrading aromatic compounds. Its gene promoter hypomethylation increases enzyme expression. Overproduction of EPHX1 reduces the transformation of testosterone to estradiol, which can contribute to PCOS. Furthermore, peroxisome proliferator-activated receptor gamma (PPAR-γ) plays a role in ovaries' function. Hypermethylation of PPARγ, hypomethylation of nuclear co-repressor 1, and alteration in acetylation of histone deacetylase 3, for which both are PPARγ co-repressors , are observed in PCOS patients showing HA. These alterations were noticed in PCOS women's granulosa cells **(4)**.

1.1.1.2. Environmental Toxicants:

Environmental Toxins: According to the United States Environmental Protection Agency (USEPA), an endocrine-disrupting chemical (EDC) is "an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behaviour"**(5)**.

EDCs can either bind to hormone receptors as agonists or antagonists. Almost everything we use on a daily basis includes an EDC **(6)**.Their phenolic or halogen chemical compositions enable them to mimic the activities of steroid hormones

According to studies women with PCOS have higher serum concentrations of EDCs. From foetal life through adolescence, prolonged and continuous exposure to EDCs can increase risk for PCOS **(7)**.

For instance, bisphenol A (BPA), a synthetic substance used in polycarbonate plastics, epoxy resins dental fillings, food and beverage packaging , infant bottles, and polyvinyl chloride (PVC), impacts metabolism through many pathways. By interacting with the G-protein coupled receptor (GPCR30), non-classical membrane ER, and oestrogen receptors (ER) and, BPA directly affects oogenesis. Additionally, it causes the secretion of androgens and suppresses the breakdown of testosterone in theca cells **(8)**.

The overproduction of androgens caused by P450c17 (17-hydroxylase), P450scc (cholesterol side-chain cleavage enzyme), and SAR1 (steroidogenic acute regulatory protein) dysregulation is another consequence of BPA on interstitial theca cells. When BPA interacts with granulosa cells, it inhibits the expression of the aromatase enzyme and oestrogen synthesis. Finally, it disrupts the intrafollicular environment and impairs the maturation and development of the oocyte. Downregulation of the enzymes testosterone 2a-hydroxylase and testosterone 6b-hydroxylase in the liver and an increase in testosterone concentration are two mechanisms by which BPA indirectly affects HA **(9)**.

The concentration of free testosterone rises as a result of BPA's replacement of testosterone as a strong ligand for the sex hormone-binding globulin (SHBG). The relationship between testosterone and BPA is reciprocal; excess androgen impairs liver clearance of BPA by inhibiting the enzyme uridine diphosphate-glucuronosyl transferase. High levels of free BPA are produced during this process, which also enhances its harmful effects on the ovaries **(10)**.

BPA is also thought to have obesogenic properties. Its obesogenic effects include adipogenesis-related gene upregulation, stimulation of adipocyte differentiation, potentiation of lipid accumulation in cells incorporated in medical syndromes, and activation of target cell conversion to adipocytes via phosphatidylinositol 3-kinase pathway**(11)**.

The stimulation of the glucocorticoid receptor causes adipogenesis in response to BPA. Adipogenesis is triggered by receptor activation because it increases the activity of the enzyme that converts cortisone to cortisol. Additionally, BPA triggers the release of the inflammatory proteins interleukin-6 (IL-6) and tumour necrosis factor-a (TNF-a), both of which affect IR and adiposity. Additionally, it inhibits the release of adiponectin and the substance that is helpful in protecting against IR **(12)**.

By directly affecting the pancreatic cells, it can also alter glucose homeostasis. By influencing the mitochondrial activity and metabolic pathways of -pancreatic cells, BPA produces a chronic rise in insulin and additional IR in long-term exposure . BPA inhibits the intracellular calcium ion fluctuation pattern with a lack of glucose condition, which lowers glucagon secretion**(13)**.

Another class of chemicals that have an impact on body health is the advanced glycation end products (AGEs), also known as glycotoxins. Pro-inflammatory molecules known as AGEs interact with the RAGE (receptor for AGE) on their surface to activate pro-inflammatory pathways and oxidative stress. Exogenous substances or nonenzymatic glycation and oxidation of proteins and lipids are two ways that AGEs might enter the body. Patients with PCOS have been found to have elevated serum AGE concentrations. Through the ERK1/MAPK pathway, AGEs halt the growth of pre-ovulatory follicles and harm follicles by inducing oxidative stress in response to interactions with RAGEs. Inflammatory chemicals within cells are increased by this interaction **(14)**.

Glycotoxins are probably capable of initiating adipogenesis, according to in vitro research on the 3T3-L1 cell line. On the other hand, a lower body mass index is associated with higher levels of soluble RAGEs, which are necessary for the removal of glycotoxins and the deposition of AGEs in the reproductive system, particularly in the ovaries. Inflammatory processes and the metabolic syndrome in PCOS are further worse by this bilateral relationship. AGEs also have an impact on IR. These substances interfered with glucose transport in the human granulosa KGN cell line and inhibited adipocyte glucose uptake in earlier studies. They also include IR because they result in oxidative stress, inflammation, and protein glycation, all of which significantly reduce

insulin sensitivity. Furthermore, AGE concentration increases alter the insulin signalling pathway and obstruct the translocation of glucose transporter 4 (GLUT-4) **(15)**.

1.1.1.3.Physical and Emotional Stress:

Although there is little research on the role of stress in PCOS, it is known that PCOS has a negative impact on mental and emotional health. Adipocytes become hypertrophied and hyperplastic as a result of chronic stress. The influence of glucocorticoids on pre-adipocyte maturation causes this behaviour. Adipokine release, stromal fat immune cell recruitment, and activation are also linked to chronic stress **(16)**.Along with altering the equilibrium between oxidants and antioxidants, it also contributes to the development of an inflammatory disease by raising levels of inflammatory cytokines including IL-6 and TNF-. Chronic stress also contributes significantly to IR.

Cortisol is released by the hypothalamic-pituitary-adrenal (HPA) axis in response to stress. By promoting visceral fat accumulation, gluconeogenesis, and lipolysis, cortisol causes IR. Furthermore, cortisol stimulates the liver to produce glucose. Additionally, stress influences how much insulin is produced. AMH inference and fluctuating sex hormone levels are two additional stress factors that may affect PCOS**(17)**.

1.1.1.4.Diet:

Although it's uncertain whether nutrition has a role in PCOS, studies have found a connection between some nutrient levels and PCOS indices.

Intake of saturated fatty acids (SFAs) contributes to PCOS by increasing inflammation and decreasing insulin sensitivity. By causing a rise in TNF- levels in the blood and the expression of a particular cytokine suppressor, SFA consumption causes inflammation.

Lack of vitamin D may make PCOS or the comorbidities it causes worse. The mRNA and protein levels of insulin receptors are upregulated by calcitriol. Both directly and indirectly, it raises insulin sensitivity. By activating PPAR-, a receptor involved in the metabolism of fatty acids in adipose tissue and skeletal muscle, the direct impact takes place. The indirect effect is the control of intracellular calcium, which is necessary for insulin-mediated signalling in adipose tissue and muscle. Conversely, a vitamin D deficiency can lead to insulin resistance by inducing an inflammatory response. In addition, vitamin D suppresses the AMH promoter **(18)**.

1.1.2. Internal Factors:

1.1.2.1. Insulin Resistance:

IR stands for an inadequate response of cells to insulin. IR has been documented in lean patients as well because it is unrelated to the adiposity, body fat topography, and androgen levels of patients. Although skeletal muscles, adipose tissue, and the liver lose their sensitivity to insulin, adrenal glands and the ovaries remain sensitive, it should be noted that IR is tissue-selective in PCOS women**(19)**.

Insulin directly stimulates the growth and synthesis of androgens in ovarian theca cells. By activating its receptors in the follicular membrane cells, insulin efficiently promotes ovarian follicle development and hormone secretion. Additionally, it stimulates ovarian P450c and P450scc enzyme activity to support ovarian steroidogenesis and raises them in conjunction with chorionic gonadotropin's synergistic effect. This hormone interacts positively with luteinizing hormone as well as insulin-like growth factor 1 (IGF-1). LH-binding sites and the androgen-producing response to LH are both increased by hyperinsulinemia. Steroidogenic acute regulatory enzyme and CYP450c17 mRNA expression are improved by LH and insulin interaction. Androgen synthesis involves CYP450c17. The productive enzyme responsible for producing androstenedione and testosterone, CYP17A1, is also increased independently by IR**(20)**.

On the other hand, hyperinsulinemia raises blood levels of free testosterone through decreasing hepatic SHBG. In addition, liver synthesis of IGF-1 binding proteins is inhibited by hyperinsulinemia. The production of androgens in thecal cells is initiated by IGF-1. A higher level of this substance in the bloodstream causes increased production of androgens in the adipose cells when IGF-1 binding protein production is inhibited. Additionally, IGF-1 upregulation lowers a particular miRNA, which speeds up granulosa cells' apoptosis and prevents folliculogenesis. The development of follicles is halted by

both HA 46 and hyperinsulinemia. Menstrual irregularity, anovulatory subfertility, and the accumulation of immature follicles are all blamed for this standstill **(21)**.

Furthermore, through influencing the pituitary gland, hyperinsulinemia plays a role in PCOS. The pituitary gland's LH is released when excessive insulin stimulates its receptors. Insulin accumulation influences both frequency and amplitude, which promotes the release of GnRH and LH. Pituitary gonadotropin sensitivity to GnRH and hyperinsulinemia both exacerbate the indirect effects of insulin on PCOS**(22)**.

The impact of insulin on adipose tissue and inflammation is yet another crucial aspect of PCOS aetiology. Fat accumulation is caused by insulin's stimulation of adipogenesis and lipogenesis and inhibition of lipolysis. The liver and adipose tissue are affected by increased plasma levels of free fatty acids (FFAs) brought on by IR. Additionally, IR lowers omentin levels without regard to the patient's body mass index (BMI). Additionally, by causing mononuclear cells (MNCs) to produce TNF-, hyperglycemia can cause inflammation **(23)**.

1.1.2.2. Hyperandrogenism:

In most cases, hyperandrogenism (HA) lowers the SHBG level, increasing the level of free testosterone. It was shown that PCOS women have greater plasma testosterone concentrations, which are capable of being converted to estrone in adipose tissue. Ovulatory dysfunction is brought on by an increased change of estrone to estradiol, which affects follicle formation and raises the LH to FSH ratio **(24)**.

Ovulation and the growth of follicles can be inhibited by HA by upregulating AMH, which works through a separate mechanism. IGF-II levels are also inversely correlated with androgen levels, and HA lowers IGF-II levels in follicular fluid. Estradiol content in follicular fluid and follicle diameter had a favourable relationship with IGF-II. Additionally, HA indirectly raises LH. Through negative feedback, estradiol and progesterone cause the release of GnRH and LH. LH levels are raised as a result of HA's disruption of the inhibitory feedback on secretion. Progesterone receptor transcription is hampered by interactions between androgen and its receptor. Additionally, this receptor is involved in the conversion of large amounts of androgens into substances that regulate

GABAA. Modulation of the GABAA receptor decreases the response to adverse progesterone feedback while activating GnRH neurons. HNF-4 induces SHBG expression by binding to its promoter, and it is hypothesised that androgens lower HNF-4 levels via blocking lipid synthesis **(25)**.

IR, inflammation, and oxidative stress are just a few of the other important aspects of PCOS that HA influences.

GLUT-4 expression, decreased insulin sensitivity, and an inhibition of insulin breakdown in the liver are only a few of the ways that HA exacerbates IR. A subset of skeletal muscle fibres with inadequate insulin sensitivity is also increased by HA. On the other hand, central adiposity, which is implicated in IR, is made worse by HA. Additionally, it was found that testosterone activates some signalling pathways in 3T3-L1 adipocytes to increase inflammatory chemicals like lipopolysaccharide-induced IL-6. By making MNCs more sensitive to glucose and escalating glucose-stimulated oxidative stress, androgen is one factor contributing to oxidative stress. It is important to note that the androgen dehydroepiandrosterone reduces interferon (IFN), a crucial regulator of healthy ovarian physiology and cell activity**(26)**.

Additionally, studies on PCOS women confirmed that their adipose tissue resembles that of men, which supports the impact of HA on adipose tissue dysfunction. Adipocyte enlargement and subsequent harm to adipokine secretion are also caused by HA**(27)**.

1.1.2.3. Inflammation:

Oocyte development and ovulation are critically dependent on appropriate inflammation. However, PCOS has been linked to elevated levels of white blood cells, C-reactive protein (CRP), and other inflammatory biomarkers in peripheral blood. HA is brought on by inflammation. A pro-inflammatory molecule called TNF- may make IR worse. Pro-inflammatory chemicals' interaction with insulin signalling pathways and decreased GLUT-4 expression both contribute to IR. According to certain research, insulin receptor signalling is inhibited by the serine residue phosphorylation of the insulin receptor substrate (IRS). Because of this mechanism, GLUT-4 translocation and glucose

reuptake are prevented. TNF- has demonstrated an in vitro potential to promote the proliferation of theca cells. IL-1 also interferes with the LH and FSH receptors. The growth of follicles and ovulation are inhibited when these receptors are blocked. By various mechanisms, TNF- and IL-1 both prevent HNF-4 from becoming activated**(28)**. Additionally, NLRP3 inflammasomes cause ovarian fibrosis, follicular pyroptosis, and disruption of follicular formation. Another reason for IR in tissues that are sensitive to insulin is a rise in CRP levels. Increased pro-inflammatory substances released by the liver and monocytes are the cause of IR. This increase in secretion is induced by CRP. Additionally, a different investigation confirmed that granulosa cells had an elevated quantity of IL-6 mRNA**(29)**.

1.1.1.4. Oxidative Stress:

An imbalance between pro-oxidants and antioxidants causes oxidative stress (OS). Reactive oxygen species (ROS) (such as O2, H2O2, and OH) and reactive nitrogen species (RNS) are examples of oxidative molecules. ROS is involved in a number of systems, including RNS , cell growth and differentiation, and signalling pathways. RONS also influences ovaries' steroidogenesis-related processes, and the feeding-related neurons that control appetite. Vital molecules including lipids, proteins, and DNA are damaged in a variety of ways when oxidative chemicals are produced in excess **(30)**.

In numerous investigations patients with PCOS showed increased OS. Nuclear factor-kappa B (NF-B) is activated when OS levels are elevated. The impact on IR and PCOS was previously discussed. NF-B is implicated in inflammatory pathways and influences the production of pro-inflammatory cytokines such TNF- and IL-6. The release of TNF- is likewise increased by a high OS level. As opposed to the usual tyrosine phosphorylation of IRS, elevated OS activates certain protein kinases that cause serine/threonine phosphorylation. As a result, OS results in IR and the insulin signalling pathway is blocked. OS contributes to obesity as well. It boosts pre-adipocyte proliferation and adipocyte differentiation by expanding mature adipocyte size. OS has a significant impact on obesity as well**(31)**.

1.1.2.5. Obesity:

A major factor in low-grade chronic inflammation is obesity. Adipocyte buildup in visceral fat promotes necrosis and subsequent hypoxia, which results in the release of inflammatory cytokines. An inflammatory state results from adipocyte death brought on by hypertrophy. Adipose tissue mononuclear cells secrete pro-inflammatory cytokines. The inflammatory disease is also brought on by excess abdominal fat.

In addition, obesity contributes to the development of IR, HA, and hyperinsulinemia. Blood levels of non-esterified fatty acids (NEFAs) rise as a result of visceral obesity. NEFAs are used by skeletal muscles instead of glucose as an energy source. A pancreatic fast response and hyperinsulinemia are caused by this hyperglycemia. Additionally, the visceral fat's lipolytic response to catecholamines results in lipotoxicity 44 and a reduction in insulin activity and clearance **(32)**.

FFA inhibits tyrosine phosphorylation while promoting IRS-1 serine/threonine phosphorylation. Increased FFAs decrease the sensitivity of intramyocellular lipids to insulin and glucose absorption. It is noteworthy that visceral fat has a higher IR weight than abdominal or subcutaneous fat perhaps due to the more severe visceral fat lipolytic response to catecholamines. The increased function of the 3 and higher expression of the 1 and 2 receptors are the causes. Additionally, the type 1 isoenzyme of 11-hydroxysteroid dehydrogenase (11-HSD), which is highly expressed in adipose tissue, particularly visceral adipose tissue, is responsible for converting cortisone into active cortisol. In omental adipocytes, glucocorticoids inhibit insulin signalling and glucose uptake. Additionally, visceral fat secretes less adiponectin than subcutaneous fat, which results in decreased adiponectin secretion in obese people**(33)**.

In addition to the previously listed tasks, adipose tissue also has an endocrine function and secretes substances known as adipokines or adipocytokines. Leptin is produced by adipocytes, and a high concentration of it prevents granulosa cells from expressing aromatase mRNA, preventing the conversion of androgens to oestrogen . Additionally, it has been hypothesised that decreased folliculogenesis is related to elevated leptin levels. Additionally, adipocytes release adiponectin, which has been shown to have anti-inflammatory, anti-diabetic, and insulin-sensitizing properties **(34)**.FFA uptake and gluconeogenesis are decreased as a result of the insulin-sensitizing impact of adiponectin. Additionally, it affects the synthesis of progesterone and oestrogen, ovulation, and the reduction of GnRH secretion. Furthermore, adiponectin reduces LH secretion from the pituitary, triggers estradiol secretion in granulosa, and is associated with androgen production in ovaries. Omentin-1, another adipose tissue secreted chemical, improves IGF-1-induced progesterone and estradiol secretion in different ways, including increasing the steroidogenic acute regulatory protein and CYP450 aromatase expression and enhancing IGF-1 receptor signalling **(35)**.The enzymes that transform androstenedione into testosterone and testosterone into dihydrotestosterone are also found in adipose tissue. Androstenedione and estrone are converted to testosterone and estradiol, respectively, by 17-HSD. Adipose tissue expresses this enzyme. This mechanism causes excess adiposity to worsen HA **(36)**.Additionally, lipotoxicity, or the buildup of lipid in non-adipose tissues, results in oxidative/endoplasmic reticulum stress, which is connected to inflammation and IR. Diacylglycerol serine phosphorylates the insulin receptor to cause IR when there are too many fatty acids in the muscles and liver .Additionally, cholesterol buildup in the liver lowers HNF-4 levels, which results in less SHBG synthesis **(37)**.

1.2. Diagnosis of PCOS:

Consider two key points in an initial evaluation for PCOS in adolescents: First, PCOS is a diagnosis of exclusion. Clinicians must be aware of the other conditions to rule out and the appropriate ancillary diagnostic tests. Second, several of the characteristics of PCOS, such as menstrual irregularities, can be normal findings during puberty.

Adolescent-specific guidelines, based on the ICPE 2017 Consensus Statement, provide the following criteria for diagnosing PCOS in adolescents: irregular menses in adolescents who are at least 2 years post menarche, the presence of persistent clinical or biochemical hyperandrogenism, and exclusion of other causes of these findings**(38).**

Specific criteria for what defines irregular menses and hyperandrogenism in an adolescent are discussed in (Table 1).

Understanding these specific cations is vital to supporting early recognition of PCOS and avoiding overdiagnosis. Irregular menses Irregular menses can be normal in the early posterchild years as the hypothalamus pituitary-ovarian (HPO) axis matures. It can take up to 5 years post menarche for maturation of the HPO axis, but most adolescents will have regular ovulatory cycles within 1 to 2 years post menarche**(39).**

Based on this evidence, the guidelines define parameters of when irregular menses may be considered abnormal (Table 1). Adolescents may find it challenging to accurately track their menstrual cycle; therefore, more general guidance suggests that patients with irregular menses that persist 2 years post menarche be evaluated for PCOS**(35).**Primary amenorrhea also may be a sign of ovulatory dysfunction in PCOS in an adolescent who

otherwise has normal pubertal development**(36).**The guidelines defi ne primary amenorrhea as lack of menses by age 15 years or more than 3 years post-thelarche.

Table 1: Diagnostic criteria for PCOS in adolescents(36).

Criteria	Evaluation	Considerations
Irregular menses/ovulatory dysfunction	Comprehensive history and physical/menses tracking. Irregular menses are defined as: • From 1 to 3 years postmenarche: <21 or >45 days • From 3 years postmenarche: <21 days or >35 days, or <8 cycles per year • Menstrual cycle >90 days for any one cycle >1 year postmenarche • Primary amenorrhea by age 15 years or age 13 years with absence of menses and no secondary sexual characteristics such as breast development	Generally, patients with irregular menses must be 2 years postmenarche
Hyperandrogenism: clinical or biochemical	• Clinical hyperandrogenism • Progressive hirsutism • Complete physical examination; use validated visual scale to evaluate hirsutism • Moderate to severe acne; follow-up with evaluation for biochemical hyperandrogenism • Biochemical hyperandrogenism • Use of high-quality assays for total and free testosterone	Moderate to severe acne alone is not adequate to diagnose clinical hyperandrogenism, must use follow-up testing
Rule out other disorders of hyperandrogenism	Laboratory evaluation for pregnancy, thyroid disorders, nonclassic congenital adrenal hyperplasia, Cushing syndrome, androgen-secreting tumor	Ultrasound is not recommended to evaluate ovarian morphology*

*Ultrasound should not be used to evaluate for PCOS in patients <8 years postmenarche. Ultrasound should be reserved for evaluation of other conditions as needed, such as evaluation for structural abnormalities in primary amenorrhea.

1.2.1. Hyperandrogenism:

Findings of irregular menses must be along with evidence of excess androgens**(40).**Excess androgens can manifest as clinical and/or biochemical hyperandrogenism. Although clinical hyperandrogenism, along with menstrual irregularities, is suggestive of PCOS,

confirmation of biochemical hyperandrogenism is recommended before making a diagnosis of PCOS**(41).**

Clinical hyperandrogenism is defined by the International Consortium of Pediatric Endocrinology 2017 Consensus Statement as moderate to severe hirsutism**(42).**

Hirsutism is the presence of dark coarse hair growth in a male-like pattern (upper lip, chin, sideburns, neck, periumbilical, chest, upper back, around nipple area) **(43).**Dark hair growth on arms and lower legs is not hirsutism and may represent ethnogenetic variation. Clinicians should perform a physical examination and evaluate hirsutism with a validated numerical scale, such as the modified Ferriman-Gallway scale**(44).**

Measurement scales should be used with caution, however, because normative cutoffs for adolescents have not been established **(45).** Moderate or severe inflammatory acne that is resistant to topical treatment is suggestive of clinical hyperandrogenism, but requires follow-up testing for biochemical hyperandrogenism **(46).**

Although mild come dominance is considered a normal finding of puberty, severe inflammatory acne is uncommon and is present in less than 5% of adolescents during early post monarchal years.

Biochemical hyperandrogenism can be documented by measuring total testosterone or calculating free testosterone with a high-quality assay (liquid-

chromatography spectrometry and extraction/chromatography immunoassays) **(47).**Other laboratory tests to evaluate hyperandrogenism include androstenedione, dehydroepiandrosterone sulfate (DHEAS), and 17-hydroxyprogesterone.3These three tests are not used to diagnose PCOS, but rather to exclude other causes of hyperandrogenism such as nonclassical congenital adrenal hyperplasia, adrenal tumors, and other androgen secreting tumors.

Table 2: Diagnostic testing for adolescents with suspected(44).

Laboratory test	Indication
Beta-hCG pregnancy	Rule out pregnancy
TSH	Rule out thyroid dysfunction
17-OH progesterone	Part of testing to rule out nonclassic congenital adrenal hyperplasia
Total testosterone, free testosterone	To document hyperandrogenism, elevated in PCOS. Required for diagnosis of PCOS.
FSH, LH, estradiol	Reserved for patients with amenorrhea to rule out premature ovarian failure (high FSH, low estradiol). LH:FSH ratio of 2:1 or greater is common in patients with PCOS but is not absolute (LH and FSH levels vary in cycle) and is not diagnostic.
Prolactin	Rule out hyperprolactinemia in a patient with amenorrhea
Dehydroepiandrosterone sulfate	Part of testing to rule out nonclassic congenital adrenal hyperplasia and androgen-secreting tumors
Androstenedione	Produced in the ovaries and adrenal glands. Part of testing to rule out androgen-secreting tumors.
Fasting blood glucose, lipid panel, and A1C	Screening for metabolic components of PCOS

1.2.2.Excluding additional factors:

A diagnosis of exclusion is PCOS. Doctors must rule out illnesses like pregnancy, thyroid dysfunction, nonclassical congenital adrenal hyperplasia, and androgen-secreting adrenal or ovarian tumours that might result in irregular menstruation or an excess of androgens**(48).**

Depending on the clinical presentation, Cushing syndrome and/or hypothalamic pituitary insufficiency may also be taken into consideration**(49).**

The diagnostic laboratory tests recommended for the initial PCOS evaluation in a teen who comes with irregular menstruation and clinical hyperandrogenism are listed in (Table 2).

Sex-hormone binding globulin and anti-Müllerian hormone are two laboratory tests that are not advised for initial evaluation but are frequently discussed in the literature discussing PCOS in adult women. Elevated androgen levels contribute to greater free testosterone concentrations by suppressing sex-hormone binding globulin. If free testosterone levels are elevated, sex-hormone binding globulin levels offer extra information, but they do not serve as a PCOS diagnostic**(50).**Although research has shown a weaker link among teenagers with PCOS, elevated anti-Müllerian hormone is mentioned in the literature as a common finding in women with PCOS**(51).**

1.2.3.Ultrasound for PCOM:

Adolescent-specific diagnostic criteria do not require the presence of polycystic morphology to diagnose PCOS**(52).**Increased gonadotropin stimulation during adolescence results in increased ovarian volume and follicular maturation, resulting in the appearance of polycystic morphology that is normal in an adolescent**(53).**Guidelines state that pelvic ultrasound should not be used for the diagnosis of PCOS and that in general, evaluation of ovarian morphology is not recommended before 8 years post menarche**(54).** Additionally, transvaginal ultrasound is an invasive test that can cause significant discomfort in adolescent girls and is not recommended in no sexually active adolescents**(55).**A transabdominal approach may not be reliable, especially in adolescents with excess body weight or obesity**(56).**

1.3. Treatment:

Two main principles guide the treatment and management of PCOS in adolescents. First, lifestyle modifications are the first line of treatment for all adolescents who either have PCOS or who are determined to be at risk before confirmation of diagnosis**(57).**Second, additional treatments should be individualized to optimize symptom relief**(58).** Interventions should be patient-centered, addressing the patient's main concerns. Additionally, patient education and counseling about PCOS is vital and should be appropriate for the patient's age and culture. Discussions about PCOS may

Table 3: Recommendations and medication options for managing PCOS in adolescents(59).

Treatment or medication	Indication	Potential effect	Common adverse reactions, contraindications, special considerations
physical exercise	recommendations for weight loss in normal-weight adolescents	cycles, improved markers of cardiometabolic health	• Consider family preferences and cultural norms. • Family should be involved in lifestyle changes.
Metformin (850 mg/day up to 1 g twice a day)	Evidence of insulin resistance (regardless of BMI)	Improve insulin sensitivity, improve glycemic control, decrease BMI, decreased androgen levels, ovulation	• Common adverse reactions include GI discomfort. • Cannot be used in patients with renal or hepatic dysfunction.
Combined oral contraceptives	Menstrual irregularities	Increased production of hepatic SHBG results in less circulating androgens, normalized menstrual cycles	• Adverse reactions may include breast tenderness, headache, increased risk of VTE, increased insulin resistance. • Consider family preferences and cultural norms.
Cosmetic procedures such as photoepilation or topical eflornithine (13.9% twice a day)	Localized hirsutism	Long-term removal of unwanted hair growth	• Cost if not covered by insurance • Discomfort
Spironolactone (50-200 mg/day)	Features of hyperandrogenism that do not resolve after 6 months of combined oral contraceptives or cosmetic procedures	Reduced excess androgens	• Adverse reactions may include irregular menses, headache, hypotension, nausea, feminization of male fetus. • Contraindicated in patients with renal failure. • Monitor for hyperkalemia. • Prescribe with contraception due to fetal effects.
Flutamide (62.5 mg/day to 250 mg/day)	Hyperandrogenism that do not resolve after 6 months of combined oral contraceptives or cosmetic procedures	Reduced excess androgens	• Dose-dependent hepatotoxicity at doses greater than 1 mg/kg/day • Prescribe with contraception due to fetal effects of feminization of male fetus.

need to be repeated as the adolescent ages and should include recommendations for lifelong management and screening for comorbid conditions associated with PCOS (Table 3) **(59).**

1.3.1.Lifestyle interventions:

Healthful eating, increasing physical activity while reducing sedentary activity, and incorporating other behavior change strategies comprise the first line of therapy for adolescents who are overweight or obese**(60).**

Weight loss of 5% to 7% has been shown to result in improved menstrual regularity and reduced testosterone levels**(61).**The ICPE 2017 consensus statement does not encourage weight loss in normal-weight adolescents with PCOS, but recommends reducing sedentary lifestyles and increasing physical activity to decrease the risk of developing metabolic syndrome**(62).**Guidelines recommend a multidisciplinary approach to addressing lifestyle modifications, incorporating nutritionists, mental health practitioners, and primary care and/or specialty providers.

Education and counseling about lifestyle modifications should include families and consider family dynamics. Family readiness to change affects adolescents' motivation.

and ability to change their behaviors. Family members can provide support as adolescents set measurable, achievable lifestyle goals and track progress toward attaining those goals **(63).**Additionally, clinicians should be sensitive when discussing diet and exercise with adolescents, and have an awareness of concerns related to body image and the effect on psychologic well-being in this age group. Clinicians should focus discussions on the benefit of overall health and lifestyle modification, rather than highlighting deficits and long-term negative.

1.3.2.Pharmaceutical interventions:

Insulin sensitizers are among the recommended therapeutic measures for PCOS symptoms.

such as combination hormonal oral contraceptives, metformin as well as antiandrogenic drugs like spironolactone. In the absence of medical contraindications, medications may be prescribed singly or in combination. Critical elements of the following in mind while recommending drugs to treat PCOS among adolescents are:

• Understanding individual characteristics, preferences, and values

• Balancing risks and benefits based on what is most bothersome to the patient

• Informing patients that although no pharmaceutical treatments are approved for PCOS, off-label use of some pharmaceuticals can help to manage PCOS symptoms**(64).**

• Maintaining a holistic approach by incorporating lifestyle

Modifications are essential to any pharmaceutical management plan. The most popular insulin sensitizer is metformin. in the treatment of PCOS**(65).**Patient studies have examined its usage insulin sensitivity has improved with PCOS .resistance, enhanced glycemic management, lower body mass index, and lowered levels of excess androgen**(66).**Metformin is utilized to ovulation in infertile patients, but may not control hirsutism is not significantly affected by menstruation the range of metformin dosages used for PCOS in clinical trials daily doses of 1,500 to 2,000 mg, although no research have contrasted them.

The efficacy of various dosages in teens. Adverse responses can cause mild to moderate GI symptoms (such as nausea, vomiting, diarrhea, and abdominal discomfort) that are self-limiting**(67).** Metformin is generally regarded as secure to treat PCOS in

both alone or in conjunction with adolescents oral contraceptives that include both hormones**(65).**combined estrogen and progestin oral contraceptives Progestins are beneficial for controlling erratic menstruation and/or teenage hyperandrogenism in PCOS patients. The standard the strength of the evidence for this recommendation is weak since few studies have examined the usage of combination oral contraceptives to treat PCOS in teenagers. The Beyond that, the treatment's duration has not been assessed**(68),** but combined oral contraceptives last for 24 months. have been utilized for teenage contraception for durations that are longer than 24 months are regarded as The estrogen and progestin combination of these medications aids in regulating menstruation and provides protection of the endometrium from highly elevated levels of PCOS anovulatory periods are accompanied by circulating estrogen**.**The estrogen concentration of oral contraceptives used in combination boosts hepatic synthesis, which decreases serum testosterone levels of luteinizing hormone suppression and sex hormone binding globulin**(69).**

Teenagers need to be assessed for potential contraindications. to using combination oral contraceptives, which includes a history of venous thromboembolism (VTE), existence of thrombogenic mutations, history of migraines with aura breast cancer, cardiovascular illness, or decompensated hepatic function**(70).**The patient's overall risk of developing VTE. without warnings is minimal. Professionals believe that Combination oral contraceptives provide more advantages than disadvantages. given the low risk of VTE in teens, hazards are minimal. Antiandrogens like flutamide and spironolactone may aid in treating clinical hyperandrogenism related Despite the fact that neither treatment is recommended by the hyperandrogenism to the FDA. However, experts due to the paucity of clinical trials for the use of antiandrogens in adolescents, there is low quality data supporting their usage. Thus while prescribing, doctors should exercise caution**(70).**Guidelines suggest using a combination of oral contraceptives and/or or aesthetic treatments for hirsutism, such electrolysis or laser therapy, for six months before beginning anti-androgens**(71).** Spironolactone's effective dosages range from 100 ranging from 100 mg twice daily to 200 mg daily, with a beginning dose 25 milligrams per day**(72).**

It has been demonstrated that flutamide works. 250 mg per day, divided into two dosages, for the treatment of hirsutism doses.9 Together with effective contraception, prescriptions using antiandrogenic drugs due to the possibility of impairment of male fetuses' external genital development**(73).**

2.Conclusion:

Although the pathogenesis of PCOS is not fully understood, it is believed that different factors from epigenetic alterations to obesity, inflammation, and inactivity may aggravate this syndrome. Since there is still no certain medication or definite cure for this condition, the routine approach after advising on some lifestyle modification and supplementary tips is symptomatic therapy with plenty of agents, including contraceptives, oral antidiabetics, or antiandrogens.

The ICPE 2017 Consensus Statement provides meaningful guidance for the diagnosis and management of PCOS in adolescents. With a focus on documenting irregular menses and evaluation of clinical hyperandrogenism, these guidelines can help with early identification of PCOS during adolescence while also reducing overdiagnosis of PCOS. Experts suggest that increased attention be paid to identification and diagnosis in adolescents in order to more effectively manage PCOS and support lifestyle modifications at a younger age.1Early diagnosis and management of PCOS can address short-term complications that pose a risk to adolescents' psychosocial well-being, and may mitigate long-term complications by engaging adolescents in a lifelong management approach.9

Managing this complex condition requires a comprehensive multidisciplinary approach that often is best facilitated by pediatric PCPs. Additionally, adolescents with PCOS require guidance from their PCPs to develop the knowledge and skills needed to be advocates for their own health and reaching their individual treatment goals throughout their lifespan. Physician assistants are well positioned to ensure that adequate

screening takes place during adolescence, and also play a vital role in patient education and management of PCOS.

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