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# A Review on Polycystic Ovary Syndrome (PCOS) and Associated Diseases

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**ABSTRACT**

Polycystic ovary syndrome (PCOS) is a chronic, complex, and most common endocrine disorder observed in women of reproductive age. This syndrome is heterogeneous by nature and is characterized by a combination of signs and symptoms of androgen excess and ovarian dysfunction. It is a significant public health issue. PCOS is associated with many comorbidities and also has several long-term metabolic and other consequences. The prevalence is quite high and is increasing day by day. It is a syndrome to be prevented by awakening awareness both in health workers and patients. There are many areas of controversies starting from its diagnosis, pathogenesis, consequences, and treatment modalities. This review is an attempt to summarize the evolution of the diagnosis and current management guidelines and also to look into future approaches. An extensive search was made through the Cochrane database, available systematic reviews and meta-analyses, and recent international guidelines for providing an updated scientific overview of PCOS.

## INTRODUCTION:

Polycystic ovary syndrome (PCOS) is a chronic, complex and the most common endocrine disorder observed in women of reproductive age and it also affects adolescents (1). Up to 70% of affected women remain undiagnosed or have long delays before the condition is recognized (2). The prevalence is generally considered to be between 6-20%, depending on the definition and the population studied (1,3). This syndrome is heterogeneous by nature and is characterized by a combination of signs and symptoms of androgen excess and ovarian dysfunction in the absence of another specific diagnosis (4). Women with PCOS often present in their adolescence or early adulthood with symptoms of oligomenorrhoea or infertility (5). Although it was previously considered as a disorder of adult women, recent evidence suggests that PCOS is a lifelong syndrome, manifesting since prenatal age. It is a significant public health issue. The health risks associated with PCOS, however, go far beyond management of these features and likely extend past the reproductive years through and beyond menopause (6).Women present with diverse features including psychological (anxiety, depression, body image and impaired quality of life) (7) Reproductive (irregular menstrual cycles, hirsutism, infertility and pregnancy complications) (8) and significant metabolic features (insulin resistance, metabolic syndrome, prediabetes, type 2 diabetes mellitus and cardiovascular risk factors) (9). There is also an increased rate of weight gain and occurrence of obesity in PCOS, increasing severity of the condition, causing considerable concern for those affected and mandating attention to a healthy lifestyle (10). PCOS has the potential for serious consequences, including increased risk for the development of endometrial hyperplasia and neoplasia (11).

### Diagnostic Criteria and Its Evolution:

Due to the complexity of this disorder and various controversies, different diagnostic criteria have been proposed over last three decades. Polycystic ovary syndrome (PCOS) was first described by Stein and Leventhal in 1953 as a syndrome of oligomenorrhoea and polycystic ovaries that was variably accompanied by hirsutism, acne, and obesity (12). The first diagnostic attempt was made by the National Institutes of Health (NIH) in 1990 and included both hyperandrogenism (HA) and oligo or an ovulation, as the two criteria to diagnose PCOS after excluding other related disorders (13). The Rotterdam criteria were published by Rotterdam ESHRE/ASRM sponsored PCOS Consensus Workshop Group in 2003 which adopted polycystic ovarian morphology (PCOM) (ultrasound finding of polycystic ovaries) to

NIH criteria; out of these three criteria (HA, ovulation dysfunction, and PCOM), two are required to diagnose PCOS (13,14). Rotterdam criteria are the broadest and encompass all combinations of otherwise unexplained clinical or biochemical evidence of hyperandrogenism, evidence of oligo-anovulation, and PCOM. In 2006, Androgen Excess and PCOS Society (AE-PCOS) concluded that PCOS should be based only on two criteria, that is clinical and/or biochemical hyperandrogenism with either polycystic morphology or clinical an ovulation (14,15). This criterion encompasses otherwise unexplained hyperandrogenism with either oligo-anovulation or PCOM; and allows a diagnosis of PCOS in women with hyperandrogenism who lack anovulatory symptoms ("ovulatory PCOS"), which comprises about 10% of cases (15). The estimated prevalence of PCOS is reported to be 8.7% using the NIH criteria, rising to 17.8% under the Rotterdam criteria and 12% using the AE-PCOS definition (16). It must be emphasized that the diagnosis of PCOS is made after exclusion of other causes of androgen excess, such as non-classical congenital adrenal hyperplasia, hyperprolactinemia, androgen-secreting ovarian or adrenal tumors, hypothyroidism, Cushing's syndrome and acromegaly (17).To meet the gaps between the diagnostic criteria, in 2012, NIH Consensus (NIH and ESHRE/ASRM) recommended broader Rotterdam/ESHRE/ASRM 2003 criteria with specific identification of PCOS phenotype of all PCOS (18). According to this recommendation, two out of three criteria (hyperandrogenism, ovulatory dysfunction, and PCOM) are needed to diagnose PCOS and each case has to be classified into a specific phenotype. PCOS frequently present during adolescence. Although there are three well known criteria to diagnose PCOS, they can be difficult to translate to adolescence. The diagnosis of PCOS in adolescents in not so straightforward, since anovulation and PCOM are not sufficient criteria for this purpose. Thus, clinical and biochemical evidence of hyperandrogenism and persistent oligomenorrhoea is required, especially if the latter persists beyond two years after menarche. No diagnostic criteria exist in peri and postmenopausal women. In these cases, a PCOS diagnosis can be presumed in the presence of a well-documented history of oligomenorrhoea and hyperandrogenism during their reproductive period (14).

**Androgen excess and polycystic ovary syndrome criteria for the diagnosis of the polycystic ovary syndrome:**

1. Hyperandrogenism: Hirsutism and/or hyperandrogenemia and
2. Ovarian Dysfunction: Oligo- an ovulation and or polycystic ovaries and
3. Exclusion of other androgen excess or related disorders

Careful clinical assessment including a meticulous history, thorough physical examination, and appropriate laboratory evaluation is mandatory for diagnosis. According to the best clinical practices guideline of 2015 by American Association of Clinical Endocrinologists (AACE) and the Androgen Excess and PCOS Society (AES), free testosterone levels are more sensitive than the measurement of total testosterone for establishing hyperandrogenism and should be ideally determined through equilibrium dialysis techniques. Value of measuring levels of androgens other than testosterone in patients with PCOS is relatively low. New ultrasound machines allow diagnosis of PCOM in patients having at least 25 small follicles (2 to 9 mm) in the whole ovary and ovarian size of 10 mL remains the threshold between normal and increased ovary size. They have also mentioned that serum 17-hydroxyprogesterone and anti-Müllerian hormone (AMH) may be useful to determine a diagnosis of PCOS (19). There are some inherent weaknesses in these criteria. Methods of commercial testosterone assay differ in different laboratories and many steroid assays are inaccurate. Moreover, serum testosterone concentration undergoes episodic, diurnal, and cyclic variation. So, the documentation of hyperandrogenemia can be difficult and this is even more difficult in adolescents as mature levels are attained approximately 1 year after menarche (20). The sonographic definition of PCOM may lead to overdiagnosis, particularly with antral follicle count criteria determined by the new generation high-definition imaging techniques (21). In adolescents, anovulatory criteria must be correlated with age and pubertal stage and routine use of PCOM is not appropriate as a diagnostic criterion (14,20). Furthermore, all these criteria overlook the potential presence of the PCOS type of functional ovarian hyperandrogenism in patients who present with hirsutism, obesity, or insulin-resistance signs such as acanthosis nigricans, but who lack clinical evidence of ovarian dysfunction (22).

**Etiopathogenesis:**

The etiology of PCOS remains unclear and it is likely to be multifactorial. No single aetiologic factor fully accounts for the spectrum of abnormalities in the polycystic ovary syndrome (23). While insulin resistance (IR) and hyperandrogenism are the two key hormonal disturbances that underlie PCOS; obesity, genetic inheritance, lifestyle and environment also contribute (17). Polycystic ovaries, increased androgen levels owing to defect of the ovarian cells (most likely theca cells), and IR have hereditary components. Environmental factors either congenital or acquired include intrauterine factors such as androgen exposure and prenatal nutrition especially intrauterine growth restriction, whereas a

major postnatal factor is acquired obesity influencing the phenotype (24). Epigenetic reprogramming of foetal reproductive tissue following in utero exposure to androgens may trigger the hypothalamic-pituitary-ovarian axis of foetus leading to altered folliculogenesis and cause PCOS in later life (19). The complex interactions between these contributing factors generally mimic an autosomal dominant trait with variable penetrance. Ethnic diversity also influences the syndrome's phenotypic diversity and its prevalence. There is a higher frequency of PCOS in Spanish, Native American and Mexican women (25).

**Hyperandrogenism:** The ovarian theca cell synthesizes excessive number of androgens in response to stimulation by increased luteinizing hormone in PCOS. When the concentration of luteinizing hormone increases relative to that of follicle-stimulating hormone, the ovaries preferentially synthesize androgen (26). In women with the polycystic ovary syndrome there is a decrease in the ratio of luteinizing hormone to the follicle-stimulating hormone as they tend to have an increased luteinizing hormone pulse frequency which favors transcription of the β-subunit of luteinizing hormone over the β-subunit of follicle-stimulating hormone. This may be due to an intrinsic abnormality in the GnRH pulse generator or by the relatively low levels of progesterone resulting from infrequent ovulation in these women (27). Studies suggest that ovarian theca cells in PCOS women more efficiently convert androgenic precursors to testosterone than normal theca cells (28).

**Insulin Resistance:** Insulin Resistance (IR) or hyperinsulinemia stimulates the theca cells of the ovary and act synergistically with luteinizing hormone to produce excessive testosterone, which is responsible for the clinical symptoms of hyperandrogenism (acne, hirsutism, alopecia). Insulin also inhibits hepatic synthesis of sex hormone-binding globulin and thus increases the proportion of free testosterone while the total testosterone concentration is at the upper range of normal or only modestly elevated (25).

**Inflammation:** Inflammation is thought to play a key role in PCOS. Direct correlations have been found between increased levels of inflammation markers (CRP, ferritin, leukocyte TNF-α, IL-6, IL-18) and the development of PCOS (29). Newly emerging issues include a pathogenic correlation of the markers of iron overload with PCOS. Increased levels of ferritin and transferrin and a higher frequency of the HP2/HP2 genotype of the haptoglobin α-chain have been observed, causing a reduction of anti-inflammatory cytokines and antioxidant molecules, leading to a state of a chronic inflammatory response (30).

**Genetic Factors:** Several lines of evidence suggest that polycystic ovary syndrome is heritable. About 3%-35% of mothers and 25% of sisters of women with PCOS also have PCOS, and metabolic syndrome prevalence is high in their parents and siblings. Tan et al., emphasized the increased likelihood of IR associated with certain genes (such as INSIG2 and MC4R) and the particular impact of TCF7L2 SNP on the development of type 2 diabetes mellitus (T2DM) and body weight gain in patients with PCOS (a per-allele weight gain of 1.56 kg/m2). Fica et al. identified insulin receptor auto-phosphorylation, reduced levels of phosphatidylinositol-3-kinase in muscle tissue and visceral adiposity as probable mechanisms. The current understanding of the pathogenesis of the syndrome suggests that it is a complex multigenic disorder. However, in rare instances, single-gene mutations can give rise to the phenotype of the syndrome. Various genome-wide association studies (GWAS) of PCOS have been conducted with inconclusive results (14). These GWAS involved genes implicated in biosynthesis and activity of androgens, metabolism (such as the insulin and insulin receptor genes) and inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) genes (25). Zhao et al., found that single-nucleotide polymorphism (SNP) rs13429458 is significantly associated with familial-based risk of PCOS and association among three loci was delineated (25).

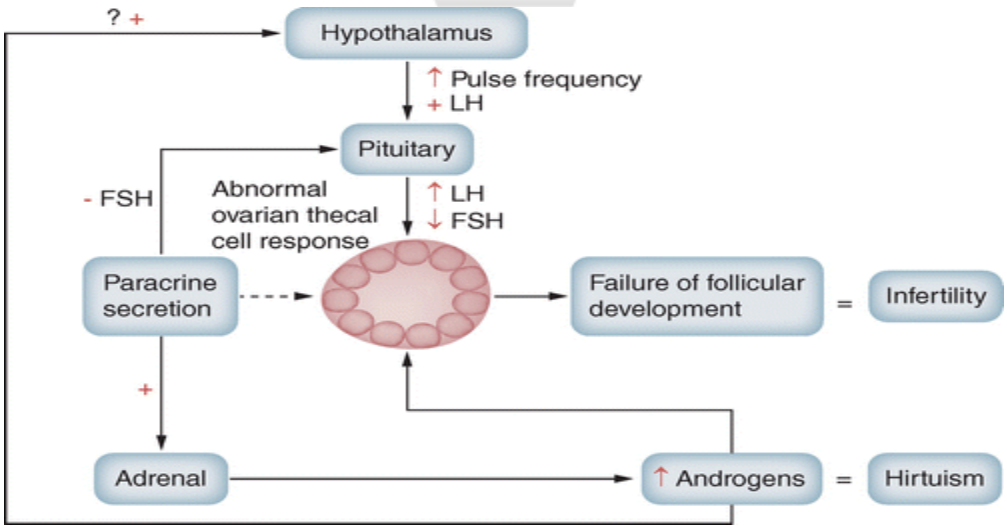


**Figure No. 1: Etiopathogenesis of PCOS**

**Clinical Features:**

Polycystic ovary syndrome is characterized by a combination of oligo/amenorrhea, clinical or endocrine signs of hyperandrogenic and polycystic ovaries. The most common abnormalities associated with PCOS include menstrual disorders (amenorrhea or oligomenorrhoea), often

leading to infertility (in 73-75% of the cases), and abdominal obesity (30-70%), and type 2 diabetes (approximately 10%) (26).

**Long-Term Health Issues and Comorbidities:** As previously stated, PCOS can cause a variety of reproductive, metabolic, psychological, and anthropometric issues in women. Insulin tolerance, dyslipidemia, and impaired glucose metabolism in the case of IGT or type 2 diabetes mellitus are all metabolic consequences of PCOS. Moreover, women with PCOS also tend to excess weight gain which exacerbates these symptoms. Cardiovascular risk factors such as chronic inflammation, oxidative stress, and impaired fibrinolysis are increased and there is evidence that cardiovascular disease (CVD) has a higher prevalence in these women. Affected women are more likely to suffer from moderate to severe depression and anxiety symptoms, low self-esteem, negative body image and psychosexual function compared to healthy women. PCOS also negatively impacts health-related quality of life (HRQL) and may limit a woman's ability to optimize a healthy lifestyle (22).

**Consequences of Metabolic Changes:** The effects of polycystic ovary syndrome go beyond fertility issues; the syndrome is linked to serious metabolic complications, which are mostly caused by obesity and insulin resistance. As a result, the polycystic ovary syndrome may be considered a sex-specific variant of the metabolic syndrome, and the word "syndrome XX" has been proposed to emphasize this connection (25). These consequences include increased risk of IGT and T2DM, dyslipidemia, systemic inflammation, non-alcoholic fatty liver disease (NAFLD), hypertension, and potential coagulation disorders (14).

**Diabetes Mellitus and Insulin Resistance:** Insulin resistance (IR) is estimated to affect 30% of lean women with PCOS and 70% of obese women with PCOS. When compared to age and weight-matched healthy people, women with PCOS have a higher risk of IR and glucose intolerance. Ethnicity appears to influence the metabolic phenotype associated with IR. Hispanic women with PCOS have a more extreme phenotype, whereas non-Hispanic black women with PCOS have a milder phenotype (15). It has been observed that the hyperandrogenic and ovulatory phenotype is the most insulin resistant, irrespective of BMI or central adiposity. Observation of a large study including 1,212 women with PCOS was that phenotype1 (all three Rotterdam criteria), is associated with more severe IR and hyperandrogenemia compared with the other three phenotypes. Phenotypes 4 (oligo or anovulation and PCOM) and 2 (hyperandrogenemia and oligo or anovulation) showed greater IR than phenotype 3 (hyperandrogenemia and PCOM) but did not differ from BMI-matched

healthy women. Adrenal hyperandrogenemia does not seem to deteriorate IR. Depending on certain risk factors, such as obesity and family history; the prevalence of IGT and T2DM in PCOS patients is 23-35% and 4-10% respectively. In lean PCOS the respective prevalence is 10-15% and 1-2% (31).

**Dyslipidemia is a condition in which the body's lipid:** Prevalence of lipid abnormalities in PCOS women is about 70% which is quite higher than healthy women. There are increased levels of low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C), with high serum triglyceride (TG) and free fatty acid concentrations, as well as decreased high-density lipoprotein cholesterol (HDL-C) levels, particularly HDL2-C, due to decreased apolipoprotein A-I (apoA-I). PCOS women also have higher concentrations of oxidized LDL-C, irrespective of BMI, which further increases CVD risk. This atherogenic profile is exacerbated by obesity and IR. Ethnic and environmental factors seem to contribute to differences in the prevalence of lipid disorders amongst PCOS women and atherogenic dyslipidemia is more profound in obese PCOS (14).

**Obesity:** Obesity is a key contributor to the clinical and metabolic manifestations of PCOS patients. The prevalence of obesity in women with PCOS was assessed in two systematic reviews and a greater risk of obesity was reported. Observation in a meta-analysis was that PCOS women are at two and three-fold higher risk of being overweight or obese, respectively, compared with their non-PCOS counterparts and this prevalence is also affected by ethnicity; higher in Caucasian than in Asian women. The body's distribution of adipose tissue is of utmost importance as abdominal obesity is an independent risk factor for CVD. The prevalence of overweight and obesity in PCOS is about 80%, with a higher BMI and waist-hip ratio (32). The key role of excess weight in worsening reproductive, metabolic, and psychological outcomes in PCOS has also been recognized in all the researches and analyses. The international guideline in PCOS recommends that BMI be assessed in all women with PCOS and that prevention of excess weight gain is vital and weight loss is recommended as the first-line treatment for overweight or obese women (17).

**Metabolic Syndrome (MSD):** Prevalence of Metabolic syndrome (MSD) is higher in PCOS patients compared with the general population (ranging from 33% to 47% in most studies, increasing to 53% in ages 30-39 years). Metabolic syndrome is associated with a five-fold higher risk for T2DM and a two-fold higher risk for CVD. There is a significant role of androgens in the pathogenesis of Mets in PCOS as the prevalence of MSD is higher in

hyperandrogenic than non-hyperandrogenic and ovulatory women with PCOS (24.8% vs 0%) (18).

**Cardiovascular Disease:** In a review by Gilbert et al. existing systematic reviews and meta-analyses were summarized evaluating comorbidities and complications of PCOS. They went through a large number of reviews (n = 23) that included 575 studies and over a million participants (1,090,072). They found women with PCOS have an increased risk of surrogate markers for CVD and a higher prevalence of CVD. Several studies indicate increased subclinical atherosclerosis in PCOS, by various indices such as increased arterial stiffness, coronary artery calcification scores, carotid artery intima-media thickness (CIMT), and endothelial dysfunction measured by flow-mediated dilation (FMD), compared with controls, even from early reproductive ages (14). But still, the association between CVD and PCOS remains controversial and findings of several prospective cohort studies are conflicting. Evidence of higher prevalence of surrogate markers of CVD predominately comes from perimenopausal women with PCOS. Almost three to four decades gap between PCOS diagnosis and CVD manifestation limits the number of large, well-phenotype cohort studies with sufficient long-term follow-up (17,21). It is suggested that well-designed, high-quality longitudinal studies are needed, specifically focusing on the association of the clinical aspects of PCOS, such as abdominal obesity and IR with CVD risk (14).

**Non-Alcoholic Fatty Liver Disease (NAFLD):** When compared to healthy women, women with PCOS have an increased prevalence (27-62%) of non-alcoholic fatty liver disease (NAFLD). Notably, an increased prevalence of PCOS has been also described in females of reproductive age with NAFLD. Insulin resistance seems to play the main pathogenetic role as it is associated with the development of NAFLD independently of obesity (BMI or waist circumference) (15).

**Hypertension and Vascular Dysfunction:** Women with PCOS seem to be at increased risk for the development of hypertension, at least in later post-reproductive life. The prevalence of hypertension is 9-25.7% in PCOS premenopausal women which is higher than the general population. Two main contributors are obesity and IR, and androgens play an independent pathogenetic role through activation of the rennin angiotensin system. Reduced vascular compliance and vascular endothelial dysfunction were noted in women with PCOS in some studies. The degree of impairment is significantly greater in obese women (16).

**Coagulation Disorders:** PCOS has been described as a potential prothrombotic state as it is associated with disturbances in the coagulation and fibrinolysis systems like increased levels of plasminogen activator inhibitor 1 (PAI-1) and fibrinogen. Increased homocysteine concentrations have also been demonstrated in PCOS, independent of BMI. Oral contraceptive pills (OCP) augment the risk of venous thromboembolism in women with PCOS (three to six-fold higher RR) as there is an inherent prothrombotic state. The risk depends on the estrogen dose and the generation of OCP (higher with 30 µg/d of ethinylestradiol and third-generation OCP). OCP may increase systemic inflammation, increase IR and alter lipid profile, by increasing TG and HDL-C and decreasing LDL-C/HDL-C ratio and may be weakly associated with increased CVD risk, although data are inconsistent and contradictory. Progestogen-only pills or hormone-releasing intrauterine devices are relatively safer. The risk is increased only when progestogen is combined with ethinylestradiol and is lowest with levonorgestrel (17).

**Infertility:** Women with PCOS may have reduced fertility due to ovulatory disorders and other endocrine abnormalities. A recent study showed that infertility is 10 times more common among women with PCOS in comparison to healthy controls. The influence of individual PCOS phenotype on female fertility remains poorly comprehended (6).

**Pregnancy Outcome:** Women with PCOS hurt pregnancy outcomes as it is suggested by an increasing body of evidence. They are at increased risk of developing gestational diabetic complications. Moreover, the foetal nutrition and endocrine environment (e.g., hyperinsulinemia) may affect foetal body weight, food intake and metabolism, with consequent long-term health in the offspring (8). Women with PCOS have an increased risk of adverse pregnancy, foetal and neonatal outcomes including preeclampsia, pregnancy-induced hypertension, preterm delivery, caesarean delivery, miscarriage, perinatal death, neonatal hypoglycemia and GDM which is in line with the current evidence-based guidelines and specialty society position statements (8,9).

**Association with Cancer:** A significant increase in risk of endometrial cancer in women with PCOS has been addressed in two systematic reviews (11). This may be the result of endometrial proliferation underlined by insulin resistance and oligomenorrhoea, prolonged endometrial exposure to unopposed estrogen in anovulation and/or related risk factors such as obesity and T2DM. Breast and ovarian cancer also have been variably associated with PCOS. PCOS patients frequently have associated obesity, anovulation, infertility, and receive

hormonal treatment for infertility. So, it is quite difficult to identify an independent risk factor for these types of cancer (25).

**Psychological Disorders:** Women with PCOS have a lower quality of life, and an increased prevalence of depressive and anxiety symptoms which has a positive correlation with higher BMI as observed in many systematic reviews and meta-analyses. This signifies the prominent role of weight reduction in the first-line management of PCOS. Weight reduction could potentially improve mood also as reported in clinical trials. The psychological problems in PCOS may relate to coping with issues such as femininity, sexuality and fertility, overweight and the nature of living with a chronic disease. International surveys suggest that most patients of PCOS are dissatisfied with long-term counseling related to medical and psychological issues (5). So, women with PCOS should be counseled appropriately about the increased risk of moderate and severe depressive and anxiety symptoms (5).

**Obstructive Sleep Apnea:** Recent studies indicate that the prevalence of obstructive sleep apnea in the polycystic ovary syndrome is higher than expected and cannot be explained by obesity alone. Insulin resistance appears to be a stronger predictor of sleep-disordered breathing than is age, body-mass index, or the circulating testosterone concentration (25).

**Screening Recommendations:**

Only to treat current symptoms is not sufficient in PCOS, but we must try to prevent any long-term morbidity. So, screening recommendations are an essential part of the management of PCOS (26).

**Type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus (GDM) screening:** All obese PCOS women and lean PCOS women over 40 years old with a history of GDM or a family history of T2DM should have an oral glucose tolerance test (OGTT), according to the European Society of Endocrinology (ESE). 6.17% The Endocrine Society and ESHRE/ASRM, on the other hand, recommend that all adolescent and adult women with PCOS undergo an OGTT because of their high risk of developing IGT and T2DM. Hemoglobin A1C (HbA1c) is not recommended as a screening test by any society. Patients with no risk factors for type 2 diabetes should be screened every 3-5 years and patients with risk factors should be screened annually. An OGTT preconception or early in pregnancy at 24 to 28 weeks gestation is recommended by a recent international guideline in PCOS (33).

**Screening for cardiovascular disease:** Despite the debates, existing international recommendations suggest that all women with PCOS be tested for CVD risk factors individually (17,21). According to the guidelines, cigarette smoking should be assessed, body weight and BMI should be measured, blood pressure should be monitored, and a full lipid profile panel should be performed. The Australian Guideline emphasizes CVD screening recommendations, such as blood pressure measurement every two years if BMI is less than 25 kg/m2 or at each visit, if BMI is less than 25 kg/m2, and lipid profile assessment every year if BMI is less than 25 kg/m2 (17).

**Psychological Well-Being Screening:** Women with PCOS should be tested at the time of diagnosis to identify possible risk factors for psychological problems. These women should be screened for not only depression and anxiety, but also for negative body image, eating disorders, and psychosexual instability, according to the 76 Guidelines. If screening is positive, further assessment by a health physician and referral to a specialist are recommended. A few studies have shown that teenagers are at an elevated risk of depression, so this population should be screened (18).

Even though NAFLD is linked to an increased risk of CVD, existing recommendations and specialty societies do not recommend regular NAFLD screening in women with PCOS at this time because long-term health results are unknown (18,19).

**Treatment:**

The treatment of PCOS focuses on the symptoms that patients typically experience. A multidisciplinary approach involving a family physician, a gynecologist, an endocrinologist, a dermatologist, a pediatrician, a nutritionist, a psychiatrist, and a psychologist should be provided as treatment. The American Task Force and the PCOS Australian Alliance Guidelines are the primary sources of care recommendations percent Other recent recommendations are also taken into account (31,32).

**Lifestyle Changes:** Lifestyle changes are regarded as a cost-effective first-line treatment option. Exercise therapy and a calorie-restricted diet are recommended as essential components of obesity control in women with PCOS, according to guidelines. A5 percent weight loss controls the menstrual cycle, increases fertility, lowers insulin and testosterone levels, reduces the severity of acne and hirsutism, and improves psychological health, according to a variety of clinical studies (31).

**Medical Treatment:** Medical treatment is added if lifestyle changes are not enough to resolve symptomatology.

**Oral Contraceptive Pills:** Oral contraceptive pills (OCP) are the most widely used drugs for the long-term care of women with PCOS, and they have been recommended as first-line treatment for hyperandrogenism and menstrual cycle disorders in women with PCOS by the Task Force and the Endocrine Society, the Australian Alliance, and the PCOS Consensus Group (18). Oral contraceptive pills (OCP) decrease LH secretions, increase sex hormone-binding globulins, and decrease free testosterone levels by suppressing the hypothalamus-pituitary-ovarian axis. This addresses hyperandrogenism-mediated symptoms; improves acne and hirsutism and corrects menstrual cycle abnormalities. A minimum of 6 months of OCP regimen is usually required to obtain satisfactory results against acne and hirsutism. Low-dose OCP that contains anti-androgenic or neutral progestins is the best choice (18).

**Metformin:** Metformin is an oral anti-diabetic biguanide drug. Even though studies show contradictory results regarding metformin effect, it is suggested as a first-line treatment for cutaneous manifestations and pregnancy complications in women with PCOS. It is also used as a combination with clomiphene citrate to improve fertility outcomes in clomiphene citrate-resistant patients (31).

**Antiandrogens:** Antiandrogens mainly act either by competitive inhibition of androgen-binding receptors or inhibit 5-alpha reductase enzyme which decreases androgen production. OCPs should be added with all antiandrogens in sexually active women as there is risk of feminization of male fetus if pregnancy occurs (19).

**Spironolactone:** It is the most effective antiandrogen which has shown a demonstrable effect on hirsutism even over and above OCPs. It is effective for acne and alopecia. It is generally well-tolerated and should be given in combination with OCP to avoid menstrual irregularity (19). But current guidelines do not provide any specific recommendations for the use of spironolactone in the management of PCOS (19).

**Cyproterone Acetate:** It is a pregestational antiandrogen. It can be used alone in dose of 50 - 100 mg daily or in combination with ethinyloestradiol. It is generally well tolerated; however, hepatotoxicity is a rare side effect. It is usually recommended for hirsutism and alopecia (19).

**Flutamide:** Flutamide is a nonsteroidal antiandrogen. Flutamide with metformin is found to be more effective than OCP alone in improving PCOS symptoms. But hepatotoxicity is a serious side effect with its use (19).

**Finasteride:** Finasteride is a potent antiandrogen and is used in combination with OCPs with better results than OCPs alone. Where estrogens are contraindicated, the combination of finasteride with spironolactone has also been tried and found effective (19).

**Cosmetic/Local Therapy:** Options available are medical therapy or physical method of removing hairs by threading, waxing, plucking, bleaching, or shaving. The permanent hair-reduction techniques, such as electrolysis, laser thermolysis and photo epilation, are also there in which destruction of hair follicles is done with an energy source (19).

**Infertility:** Treatment Both the American Task Force and the PCOS Australian Alliance Guidelines recommend clomiphene citrate as the first line treatment of anovulatory infertility. The American College of Obstetricians and Gynecologists (ACOG) has recently issued clinical management guidelines that updated the use of letrozole for ovulation induction in women with PCOS. They have advocated letrozole as first-line therapy for ovulation induction because of the increased live birth rate compared with clomiphene citrate. If clomiphene citrate or letrozole use fails to result in pregnancy, the recommended second-line intervention is exogenous gonadotropins, in vitro fertilization or laparoscopic ovarian surgery. Laparoscopic techniques that can successfully trigger ovulation include ovarian biopsy and electrocautery, laparoscopic ovarian drilling, transvaginal hydro laparoscopy, ultrasound-guided transvaginal ovarian needle drilling or laparoscopic ovarian multi-needle intervention (34).

**Treatment in an adolescent:** Till date, no placebo-controlled randomized controlled trials for the treatment of PCOS in adolescents have been conducted. Recommendations suggest individualizing treatment of adolescents with PCOS. Lifestyle modification and weight reduction are considered as part of the first-line treatment, especially in obese adolescents. The mainstay of therapy for adolescents with PCOS is OCPs. However, the best OCPs and their appropriate duration of use in adolescents are not well defined. Metformin is also widely used, yet, the necessary treatment period is still indefinite (6). Early lifestyle modifications and metformin therapy have been associated with promising preventative results (19).

**New Therapeutic:**

Options In a study by Cakir et al. women with acne received intramuscular injections of 0.5-1 mg/kg/dL isotretinoin, and the therapy was highly effective. It may be used as a first-line treatment for PCOS patients with acne, second only to oral contraceptive therapy. Isotretinoin may also improve the patients' reduced AMH levels. However, Isotretinoin therapy fails to produce the desired clinical effect in the patients with severe acne. It is expensive and contributes to an increase in body weight and triglyceride levels and not yet widely recommended in PCOS (26). A newer polytherapy was proposed recently by Vinaixaetal, including 3-month flutamide metformin-pioglitazone therapy combined with ester-progestogen treatment, which also improved the lipid profile (reduced LDL, increased HDL), higher androgen levels as well as increased carotid intima-media (CIM) thickness, which in turn prevents the occurrence of atherosclerosis and related complications. Thiazolidinedione derivatives use is another alternative that enhances insulin sensitivity. However, these drugs do not reduce androgen levels, can contribute to patients 'weight gain and are contraindicated for women wishing to become pregnant. Metformin combination therapy with new drugs glucagon-like peptide receptor agonists 1 (GLP-1) leads to more effective weight reduction lowers insulin resistance and improves reproductive function. However, they do not have a high safety profile in women of reproductive age (31). It is suggested that vitamin D deficiency has an impact on the pathogenesis of insulin resistance in PCOS and several studies have recently been published on the effectiveness of vitamin D supplementation. As lipid disorders and obesity are frequently associated with PCOS, use of statins is promising. Statins have anti-inflammatory, antioxidant, anti-proliferative and lipid-lowering effects (26). This was confirmed by the results of Celik and Acbay who demonstrated that a 12-week combination therapy with metformin in reducing the testosterone, DHEA-S, body weight, CRP, TG and LDL cholesterol. Supplementation with omega-3, α-lipoic acid and N-acetyl cysteine has antioxidant, anti-inflammatory effect, and also improves insulin sensitivity and lipid profile of women with PCOS. Increased activity of the sympathetic nervous system plays a role in the pathogenesis, progression and treatment of PCOS. Obesity, hyperinsulinemia, obstructive sleep apnea (OSA) and metabolic disorders in PCOS patients are enhanced by increased intraovarian production of nerve growth factor (NGF) and elevated muscle sympathetic nerve activity (MSNA). To combat these, the use of non-pharmacological interventions (weight reduction, continuous positive airway pressure in OSA, electro-acupuncture stimulation of baroreceptors), pharmacological treatment (insulin

sensitizers) and surgical procedures (renal denervation) can bring surprising result. Studies have shown that fibroblast growth factors (FGFs), particularly FGF 1, 10, 19 and 21 are involved in the regulation of carbohydrate and lipid metabolism, have cardioprotective activity (FGF-21), and are also responsible for the excessive activity of the sebaceous glands. An analog of FGF-21 called LY2405319is shown to reduce insulin resistance, improve dyslipidemia and reduce weight (27). Some recent clinical trials showed that Myo-inositol decreases glycemia improves the serum lipid profile and reduces the secretion of LH, DHEA, testosterone and progesterone. A high concentration of Myo-inositol in the follicular microenvironment increases the number of oocytes. Therefore Myo-inositol restores menstrual regularity, ovulation and improves fertility (28).

## CONCLUSION:

Polycystic ovary syndrome, though the commonest endocrine pathology, till date research and extensive studies are being carried out as its etiopathogenesis is still unclear, diagnostic criteria are still evolving, management is complex, and newer therapeutic options are being explored every day. Often key patient needs are not being met well, and there is a gap of knowledge in both patients and health professionals. But what is important to remember and practice is that it is a syndrome more to prevent than to treat. All providers involved in the multidimensional care of women with PCOS should be aware of its long-term health risks to provide appropriate counseling, screening, and management options.

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