WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 15, Issue 1, 1243-1270. Review Article ISSN 2277–7105

CURRENT TRENDS IN THE DIAGNOSIS AND THERAPEUTIC APPROACHES TO PCOS

Anamika Koshti*[1], Jinal Jadeja[2], Mayuri Vaja[3], Rimsha Soni[4], Priyanka Yadav[5], Dr. Divyakant Patel[6]

[1-4]Pharm D, Department of Pharmacy Practice, Sharda School of Pharmacy Gandhinagar, Gujarat, India.

[5]Assistant Professor, Department of Pharmaceutics, Sharda School of Pharmacy Gandhinagar, Gujarat, India.

[6]Professor, Department of Pharmacognosy, Sharda School of Pharmacy Gandhinagar, Gujarat, India.

Article Received on 05 Dec. 2025,
Article Revised on 25 Dec. 2025,
Article Published on 01 Jan. 2026,

https://doi.org/10.5281/zenodo.18152194

***Corresponding Author**

Anamika Koshti

Pharm D, Department of Pharmacy Practice, Sharda School of Pharmacy Gandhinagar, Gujarat, India.

How to cite this Article: Anamika Koshti*[1], Jinal Jadeja[2], Mayuri Vaja[3], Rimsha Soni[4], Priyanka Yadav[5], Dr. Divyakant Patel[6] (2026). Current Trends In The Diagnosis And Therapeutic Approaches To Pcos. World Journal of Pharmaceutical Research, 15(1), 1243-1270.

This work is licensed under Creative Commons Attribution 4.0 International license.

ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the most common and complex endocrine disorders affecting women of reproductive age, with manifestations that extend beyond reproductive dysfunction to include significant metabolic and psychological consequences. Its heterogeneous nature, variable clinical presentation, and absence of a universally accepted diagnostic standard continue to pose challenges in timely diagnosis and optimal management. This review summarizes current trends in the diagnosis and therapeutic management of PCOS, highlighting recent advances, ongoing controversies, and emerging future directions. Contemporary diagnostic approaches incorporate established criteria from the NIH, Rotterdam, and AE-PCOS Society, alongside improved hormonal assays, updated ultrasound thresholds, and growing interest in biomarkers such as anti-Müllerian hormone.

Recognition of distinct PCOS phenotypes has enhanced understanding of disease variability and supports more individualized risk assessment and treatment planning. Management strategies have evolved from a predominantly symptom-based approach to a holistic, patient-centered model. Lifestyle modification remains the foundation of care, while

pharmacological therapies now include insulin sensitizers, ovulation-induction agents, hormonal treatments, and newer metabolic drugs such as GLP-1 receptor agonists and inositols. Complementary therapies and advances in assisted reproductive technologies further expand therapeutic options, particularly for infertility. Looking ahead, precision medicine, genomics, epigenetics, and artificial intelligence hold promise for improving diagnostic accuracy and tailoring treatment to individual phenotypes. Despite progress, gaps remain in long-term outcome data and phenotype-specific interventions, underscoring the need for continued research to improve outcomes and quality of life for women with PCOS.

KEYWORDS: Polycystic Ovary Syndrome (PCOS), Diagnosis, Therapeutic approaches, Pharmacological therapy, Infertility.

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine disorders affecting women of reproductive age and continues to pose significant challenges for clinicians, researchers, and patients worldwide. Although it has been studied for decades, PCOS remains a complex and heterogeneous condition characterized by a wide spectrum of reproductive, metabolic, and psychological features. The disorder not only disrupts normal ovarian function but also exerts systemic effects that extend throughout a woman's lifespan.[1]

Recent estimates suggest that PCOS affects 8–13% of women globally, making it one of the most common causes of menstrual irregularity, anovulatory infertility, and androgen excess. However, these figures may underestimate the true burden, as many women remain undiagnosed or receive delayed diagnosis due to its diverse presentations and the lack of a single standardized diagnostic framework. This variability—both in symptoms and diagnostic criteria—complicates epidemiological assessments and often results in inconsistent clinical management across regions and healthcare settings.[2]

PCOS is increasingly recognized not only as a reproductive disorder but also as a significant metabolic condition. Many affected women experience insulin resistance, dyslipidemia, obesity, and an elevated long-term risk of type 2 diabetes and cardiovascular disease. In addition, psychological concerns such as anxiety, depression, and reduced quality of life are common yet often underaddressed. These overlapping reproductive, metabolic, and emotional challenges contribute to the substantial global health burden of PCOS.[2]

Early diagnosis plays a crucial role in managing the condition effectively. Recent trends in research emphasize improved diagnostic precision through better hormonal assays, metabolic screening, imaging techniques, and the identification of emerging biomarkers. Updated guidelines—such as those from the NIH, Rotterdam criteria, and AE-PCOS Society—have broadened diagnostic considerations, yet they also highlight ongoing debates regarding the best approach to identify PCOS, especially in adolescents and lean phenotypes.[1]

Therapeutic approaches have also evolved considerably. While lifestyle modification remains the cornerstone of care, modern management now includes a wide range of pharmacological options, from insulin sensitizers and ovulation-inducing agents to hormonal therapies and anti-androgens. Inositols, GLP-1 receptor agonists, SGLT2 inhibitors, and targeted metabolic treatments are gaining prominence. Alongside these medical therapies, complementary approaches—such as nutraceuticals, herbal formulations, acupuncture, and personalized diet strategies—are increasingly supported by emerging evidence.[1,2]

With the growing focus on individualized medicine, attention is shifting toward phenotype-specific treatment, genetic profiling, and the use of artificial intelligence to support early diagnosis and clinical decision-making. These advances open new possibilities for improving outcomes but also highlight existing challenges, such as inconsistent diagnostic practices, limited long-term data, and the need for more culturally and ethnically diverse research.[1]
This review article examines current trends in the diagnosis and therapeutic management of PCOS, summarizing recent evidence, highlighting unresolved questions, and outlining future directions aimed at improving patient-centered care.

2. Current Trends in Diagnosis

2.1 Updated Diagnostic Criteria

PCOS lacks a single universal definition, making diagnosis challenging. Over time, major international bodies—NIH, Rotterdam, and AE-PCOS Society—have proposed diagnostic systems based on three core features: ovulatory dysfunction, androgen excess, and polycystic ovarian morphology (PCOM). Differences among these criteria significantly influence diagnostic rates and the classification of clinical phenotypes.[2,3]

2.1.1- NIH Criteria (1990)

The earliest widely accepted guideline. Diagnosis requires both:

1. Chronic anovulation/oligo-ovulation

2. Clinical or biochemical hyperandrogenism

Other causes must be excluded. Ultrasound appearance is not required. These criteria identify women with more "classic" and severe PCOS—typically showing significant menstrual irregularity, hirsutism, and increased metabolic risk.[4-6]

2.1.2 Rotterdam Criteria (2003)

The most globally used criteria today. Diagnosis requires any two of the following three:

1. Oligo- or anovulation
2. Clinical/biochemical hyperandrogenism
3. Polycystic ovarian morphology on ultrasound (≥12 follicles 2–9 mm or ovarian volume >10 ml)

Other endocrine disorders must be excluded. This broader definition identifies four phenotypes, capturing women with ovulatory PCOS, non-hyperandrogenic PCOS, or ultrasound-dominant PCOS. Recent guidelines caution against diagnosing adolescents too early, because normal puberty can mimic PCOS features.[1,7]

2.1.3 AE-PCOS Society Criteria (2006)

Focuses strongly on androgen excess. Diagnosis requires:

1. Mandatory hyperandrogenism (clinical or biochemical)
2. Plus ovarian dysfunction (anovulation or PCOM)

This narrower definition identifies women with more uniform and often more metabolically severe presentations. It is commonly used in research for population consistency.[2,8]

2.1.4 Limitations of Existing Criteria

Despite advances, several gaps remain: **Overlap with normal adolescence:** Irregular cycles and PCOM can be normal in teenagers, increasing overdiagnosis risk. **Variability in androgen testing:** Hormonal assays differ across labs, causing inconsistent interpretation. **Ethnic differences:** Features of PCOS vary by ethnicity; e.g., South Asian women show stronger insulin resistance even with mild hyperandrogenism. **Outdated ultrasound cutoffs:** Modern high-resolution ultrasound detects more follicles, making old PCOM thresholds less accurate. **Metabolic dysfunction excluded:** Insulin resistance is common but not part of any diagnostic guideline. **Inconsistent use internationally:** Clinics and countries follow different criteria, creating variability in diagnosis and management.[1,6]

2.2 Phenotypes of PCOS

Based on the Rotterdam criteria, PCOS is classified into four major phenotypes, each reflecting a different combination of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (PCOM). These phenotypes differ in clinical presentation, metabolic risk, and treatment needs.[1,2,5]

2.2.1. Phenotype A (Classic PCOS: HA + OD + PCOM)

Features: Hyperandrogenism (clinical/biochemical). Ovulatory dysfunction. Polycystic ovarian morphology.

Characteristics: Most severe form. Higher levels of insulin resistance, obesity risk, dyslipidemia. Marked menstrual irregularities. Most common phenotype in South Asian populations.[2,3]

2.2.2. Phenotype B (Classic PCOS: HA + OD)

Features: Hyperandrogenism. Ovulatory dysfunction. Normal ovarian morphology. **Characteristics:** Metabolically similar to Phenotype A. Lower follicle counts on ultrasound. Strong reproductive and metabolic complications despite normal ovarian appearance.[3,7]

2.2.3. Phenotype C (Ovulatory PCOS: HA + PCOM)

Features: Hyperandrogenism. Polycystic ovarian morphology. Regular ovulation/menstrual cycles.

Characteristics: Mild reproductive symptoms. Androgen-driven symptoms (acne, hirsutism) remain prominent. Lower metabolic risk compared to Phenotypes A and B. Often underdiagnosed due to normal cycles.[1,6]

2.2.4. Phenotype D (Non-Hyperandrogenic PCOS: OD + PCOM)

Features: Ovulatory dysfunction. Polycystic ovarian morphology. No clinical or biochemical hyperandrogenism. **Characteristics:** Mildest phenotype, Lower cardiometabolic risk, More commonly confused with normal physiological variations, especially in adolescents, Debate exists whether this should be classified as “true” PCOS due to absence of androgen excess.[1-3]

2.2.5. Clinical Importance of PCOS Phenotyping

Helps predict metabolic risk—Phenotypes A and B show the highest risk. Guides treatment choices, e.g., ovulation induction vs. androgen-lowering therapies. Essential for research, as

heterogeneity affects study outcomes. Useful for counseling patients regarding fertility, weight management, and long-term complications.[4,9]

2.3 Clinical Manifestations

PCOS presents with a combination of androgen excess, ovulatory dysfunction, and metabolic abnormalities, with symptoms varying across phenotypes and age groups.

2.3.1 Hyperandrogenism: Clinical: Hirsutism, acne, androgenic alopecia. **Biochemical:** Elevated testosterone, DHEAS, androstenedione; low SHBG.

2.3.2 Menstrual & Ovulatory Dysfunction: Oligomenorrhea, amenorrhea, irregular cycles. Anovulation leading to infertility or reduced fertility.

2.3.3 Metabolic Features: Insulin resistance and hyperinsulinemia. Dyslipidemia, central obesity, NAFLD. Increased risk of type 2 diabetes and metabolic syndrome.

2.3.4 Reproductive Issues: Difficulty conceiving due to anovulation. Higher risk of early pregnancy complications and endometrial hyperplasia.

2.3.5 Dermatological Findings: Acanthosis nigricans, skin tags, seborrhea.

2.3.6 Psychological Manifestations: Anxiety, depression, body image concerns, and higher rates of eating disorders.[1,2,3,10]

2.4 Role of Imaging in PCOS

Imaging plays an important supportive role in diagnosing PCOS, especially for identifying polycystic ovarian morphology (PCOM). While it is not mandatory for diagnosis in all criteria, it provides valuable information about ovarian structure, follicle count, and overall reproductive health.

2.4.1 Transvaginal Ultrasound (TVUS): Primary Imaging Tool

Transvaginal ultrasound is the gold standard for assessing ovarian morphology in adults.

Key features of PCOM: ≥20 follicles per ovary (2–9 mm) with modern high-resolution probes. Ovarian volume >10 mL. “String-of-pearls” appearance due to peripheral follicle arrangement. Increased stromal density and stromal echogenicity. Advantages: High image resolution. Excellent visualization of antral follicles. Cost-effective. Widely available. **Limitations:** Not preferred or feasible in adolescents, virgins, or some cultural contexts.[11]

2.4.2 Pelvic Ultrasound (Transabdominal)

Used when TVUS is not suitable (e.g., in adolescents). **Pros:** Non-invasive. Useful for screening. **Cons:** Lower sensitivity. Follicle counts may be underestimated. BMI and bladder filling can affect clarity. Because of these limitations, experts (AAFP, JCEM) caution against diagnosing PCOS in adolescents based solely on ultrasound.[11]

2.4.3 Emerging Imaging Technologies

2.4.3.1 3D Ultrasound

3D ultrasound provides: More accurate follicle count and volume measurement. Better assessment of stromal tissue. Improved reproducibility across observers. This technique helps reduce misdiagnosis caused by variability in 2D ultrasound.

2.4.3.2 Doppler Ultrasound

Doppler evaluates ovarian blood flow and stromal vascularity. Findings in PCOS may include: Increased stromal vascular flow. Higher ovarian stromal blood volume. Although promising, Doppler indices are not yet incorporated into standard diagnostic criteria.

2.4.4 Modern Challenges in Imaging-Based Diagnosis

As ultrasound technology improves, the threshold for follicle count (originally 12 follicles) has become outdated. Updated guidelines now recommend ≥20–25 follicles per ovary depending on probe frequency. Over-reliance on imaging in adolescents can lead to overdiagnosis, as multifollicular ovaries can be normal during puberty. Therefore, imaging should be interpreted alongside clinical and biochemical features, not in isolation.[3,511]

2.5 Biomarkers and Laboratory Investigations

Laboratory testing in PCOS focuses on confirming hyperandrogenism, assessing ovarian function, and identifying metabolic risks. Hormonal markers include total and free testosterone, SHBG (usually low), DHEAS, and sometimes an elevated LH/FSH ratio. AMH is often high in PCOS and can support diagnosis when ultrasound is unclear. Metabolic markers check for insulin resistance and cardiometabolic risk. These include fasting insulin, HOMA-IR, oral glucose tolerance test (OGTT), HbA1c, and a full lipid profile. Dyslipidemia and impaired glucose tolerance are common findings. Emerging biomarkers such as kisspeptin, adipokines (adiponectin, leptin), inflammatory markers (CRP, IL-6), and certain microRNAs are being studied, but they are not yet used for routine diagnosis. Overall, these

tests help differentiate PCOS from other endocrine conditions, detect hidden metabolic issues early, and guide personalized treatment.[1-5,11]

2.6 Screening for Associated Comorbidities

Screening for associated comorbidities is an essential component of PCOS management because the syndrome is closely linked to multiple metabolic, endocrine, and psychological disorders. All women with PCOS should be evaluated for insulin resistance and glucose intolerance, as these abnormalities can progress to type 2 diabetes; fasting glucose, HbA1c, and preferably a 2-hour OGTT are recommended for accurate detection. A complete lipid profile is required to assess dyslipidemia, particularly elevated triglycerides and low HDL, which significantly increase cardiovascular risk. Regular monitoring of blood pressure and assessment of BMI, waist circumference, and waist-hip ratio help identify obesity and central adiposity, both of which exacerbate hormonal and metabolic dysfunction. Thyroid screening, especially TSH and free T4 levels, is advised to rule out hypothyroidism, a condition that frequently coexists with PCOS and can worsen menstrual irregularities. Evaluation for non-alcoholic fatty liver disease (NAFLD) using liver enzyme levels or ultrasound is important because hepatic steatosis is common in insulin-resistant PCOS patients. Additionally, screening for obstructive sleep apnea, particularly in overweight individuals, is recommended due to its association with cardiometabolic disturbances. Psychological assessment for depression, anxiety, and reduced quality of life is also crucial, as mental health disorders are highly prevalent and often underdiagnosed in this population. Comprehensive comorbidity screening ensures early identification of complications and allows for a multidisciplinary, preventive approach to long-term PCOS management.[1-4,9-11]

3. Current therapeutic approaches in PCOS

3.1 Lifestyle Intervention

Managing overweight and obesity in women, especially those with PCOS, starts with improving diet and increasing physical activity, which can also enhance menstrual regularity, fertility, and insulin sensitivity. Care should consider individual lifestyle and mental health factors like anxiety, depression, and body image. Evidence shows that diet, exercise, and relaxation techniques can improve metabolic and reproductive hormones in women with this common endocrine disorder.[12]

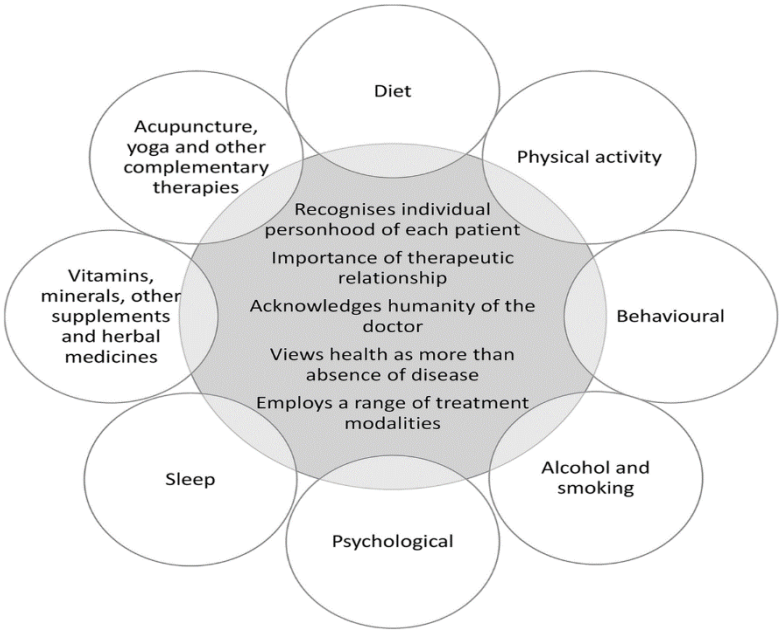

Figure 1: Holistic care looks at the whole person, not just the complaint. It values a strong croaker. Case relationship where cases are active in their own care. Health is seen as overall well- being, including internal, emotional, social, and physical aspects. Care uses multiple, well- coordinated treatment approaches rather than one system alone.[13]

Women with PCOS are encouraged to adopt healthy lifestyle habits to maintain weight and overall health.[13] For those with excess weight, a 5–10% reduction through a 30% energy deficit (1200–1500 kcal/day) is recommended, though lifestyle improvements are beneficial even without weight loss.[13] Losing over 5% of body weight can enhance fertility, reduce ovarian volume, and improve metabolic and hormonal factors like glucose control, insulin sensitivity, and androgen levels.[14-16] However, response varies, with only about one-third achieving full symptom remission, especially in women with higher waist circumference or elevated androstenedione.[17] Targeting insulin resistance and central fat can provide additional benefits independent of weight loss.[16]

Dietary recommendations for women with PCOS should consider individual lifestyle and preferences, following general population guidelines.[18] Reducing carbohydrate intake is the most studied dietary approach and has been shown to improve intermediate outcomes in PCOS, supported by recent systematic reviews.[19,20] Higher protein intake may be more effective than carbohydrate-rich diets in lowering androgens, as high-protein meals reduce postprandial insulin and dehydroepiandrosterone levels.[21] The type of dietary fat is also important, with mono- and polyunsaturated fats improving metabolic dysfunctions and high-fat meals lowering post-meal testosterone due to slower nutrient absorption.[22] Overall, both

macronutrient composition and fat quality play key roles in managing metabolic and hormonal factors in PCOS.

3.2 Pharmacological therapy

This includes the "traditional" and "first-line" agents long used in PCOS management: insulin sensitizers, ovulation-induction drugs, hormonal treatments, and symptomatic therapy.

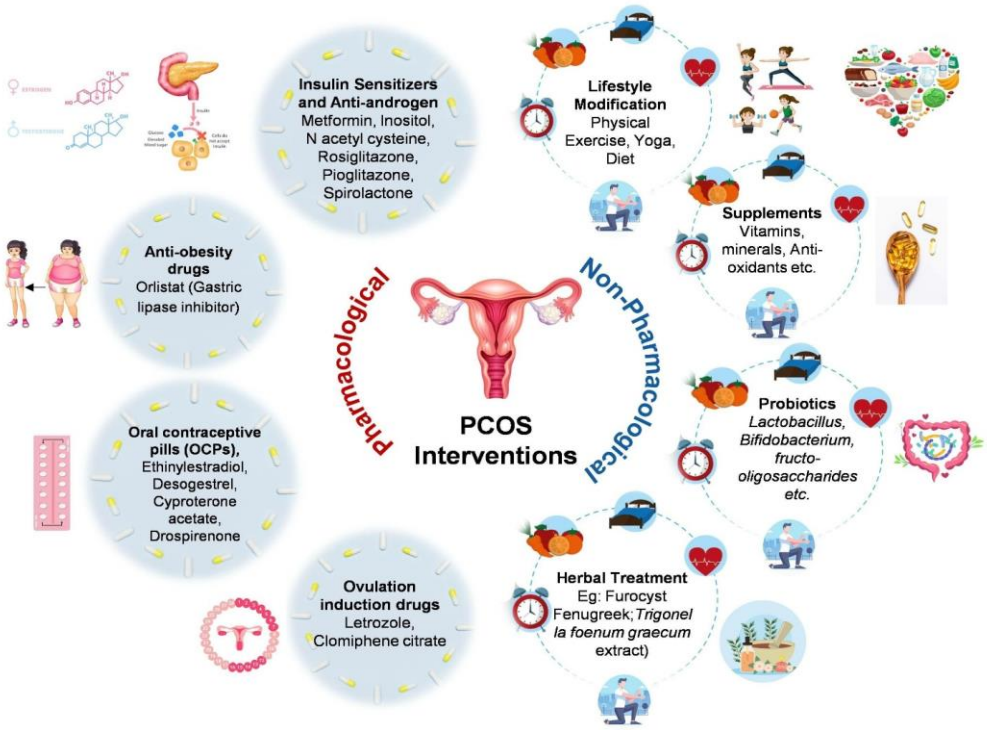

Figure 2: (23) This figure shows how managing PCOS works best when you care for the whole person—not just the symptoms. Medical treatments can help balance hormones, improve insulin sensitivity, support healthy weight, and encourage regular ovulation. At the same time, lifestyle habits like eating a balanced diet, staying active, practicing yoga, and using supplements, probiotics, or herbal remedies can boost overall well-being. When these medical and lifestyle approaches come together, they help restore hormonal balance, improve metabolism, and enhance quality of life for women living with PCOS.

3.2.1 Insulin sensitizers

Metformin is a first-line antidiabetic therapy widely used in PCOS due to its insulin-sensitizing effects.[24] PCOS is driven by insulin resistance, making medications like metformin, GLP-1 receptor agonists, and DPP-4 inhibitors important for management.[24] Metformin is the most studied, especially for women with insulin resistance or metabolic

syndrome caused by metabolic disturbances.[25] However, not all women ovulate with metformin alone, so additional treatments may be needed.[26] Hyperinsulinemia stimulates androgen overproduction in theca cells, inhibiting follicle development and causing polycystic ovarian morphology.[27,28] Insulin sensitizers such as metformin and thiazolidinediones (TZDs) improve ovulation by reducing insulin resistance and androgen levels.[29,30] Metformin also supports lifestyle-independent weight loss and improves hepatic dyslipidemia and hyperinsulinemia. TZDs like pioglitazone decrease fasting insulin and free androgens while increasing SHBG.[27,30] Inositols, including myo-inositol and D-chiro-inositol, enhance insulin signaling, restore FSH/LH balance, improve oocyte quality, and reduce hyperandrogenism. These therapies collectively target metabolic and reproductive dysfunctions, improving clinical outcomes in women with PCOS.

3.2.2 Oral contraceptives and Anti-Androgens

Oral contraceptives are the first-line treatment for menstrual irregularities and hyperandrogenism in PCOS, as they lower LH and increase SHBG, reducing androgen production and activity. This improves hirsutism, acne, and menstrual cycles. Anti-androgen agents like spironolactone, cyproterone acetate, flutamide, and finasteride further block androgen action and enhance metabolic and lipid profiles. Combining oral contraceptives with anti-androgens effectively manages PCOS symptoms, but careful patient screening is essential to avoid adverse outcomes.[31]

3.2.3 Ovulation Inducers

Ovulatory dysfunction is a key feature of PCOS, and women desiring fertility often require ovulation induction. Anovulation results from low FSH and disrupted follicle maturation influenced by LH, androgens, and insulin. First-line treatments include clomiphene citrate (CC) to increase FSH and low-dose gonadotropins to promote mono-follicular development.[32] Aromatase inhibitors like letrozole enhance ovulation by increasing GnRH and FSH, favoring mono-follicular ovulation without negative effects on the endometrium.[33]

3.2.4 Emerging Metabolic Agents

Incretin hormones (GLP-1 and GIP) regulate glucose-dependent insulin secretion, but insulin resistance can impair their action, as seen in some women with PCOS.[34] GLP-1 receptor agonists improve insulin sensitivity mainly through weight reduction, modulation of inflammatory insulin signaling, and β-cell function regulation.[34] Clinical studies show these agonists lower BMI—particularly abdominal fat—reduce insulin resistance, and decrease

testosterone levels, often outperforming metformin.[34] They also improve overall quality of life for patients.[34] Dual GLP-1 and GIP receptor agonists (twincretins) appear even more effective in combating obesity and metabolic dysfunction, making them promising for PCOS management once supported by clinical studies.[35]

3.2.5 Adjunctive and Novel Therapies

PCOS management can be enhanced with statins, which inhibit HMG-CoA, lowering cholesterol, ovarian androgen production, inflammation, oxidative stress, and insulin resistance. Atorvastatin shows greater benefits when combined with metformin.[36] Statin therapy has been shown to reduce androgens, improve lipid and inflammatory profiles, increase insulin sensitivity, and alleviate PCOS symptoms.[37] Additionally, vitamin D acts on pancreatic and muscle cells to modulate AMH signaling, follicle sensitivity to FSH, progesterone secretion, and glucose regulation, supporting reproductive and metabolic functions in PCOS.[38]

3.3 Complementary and alternative therapies

Herbal medicines can improve metabolic function, insulin sensitivity, hormonal balance, and overall health in women with PCOS. They help address insulin resistance, metabolic dysfunction, and hormonal imbalances.[39] Herbs like cinnamon, curcumin, sage, fennel, and certain Chinese herbals may perform as well as or better than metformin or clomiphene citrate. These herbs reduce inflammation, lower androgens, and improve insulin response. However, more research is needed to determine optimal dosage, duration, and clinical use.[40]

3.4 Fertility management in PCOS

Infertility affects 10–15% of couples worldwide and carries significant emotional and psychological costs, including loss of social and familial wellbeing.[41] Assisted reproductive technologies (ART) such as IVF, pre-implantation genetic testing, and embryo cryopreservation have improved reproductive outcomes.[42] Despite these advancements, patients still experience emotional hardship, depression, and relationship strain during treatment cycles. Those with medical complications may face loss of reproductive autonomy and heightened distress. Integrating mental health support with ART is essential to address psychosocial consequences and improve patient outcomes.[43]

3.4.1 Ovarian drilling

Ovarian drilling is a second option when medical treatment fails. It leads to spontaneous ovulation rates between 30 and 90 percent and pregnancy rates from 13 to 88 percent. New techniques have been created to reduce surgical risks while keeping effectiveness.[44] We conducted an electronic database search using PubMed, Medline, and Embase up to March 2022. We developed a search algorithm that included the terms "polycystic ovary syndrome," "infertility," "clomiphene citrate," "gonadotropin," "laparoscopy," "ovarian drilling," "transvaginal hydrolaparoscopy," and "ovulation induction." Two coauthors, A.M. and L.D.C., carried out the search analysis.[45,46]

3.4.2 IVF/ICSI advancement

ICSI (Intracytoplasmic sperm injection) began as a treatment for severe male-factor infertility, but it is now being used excessively around the world. Even though its use has increased, evidence does not indicate better outcomes compared to conventional IVF in cases of non-male-factor infertility. Guidelines suggest limiting ICSI to cases with severe sperm defects or previous fertilization failures, since it is more invasive, expensive, and might also carry greater safety risks. Therefore, it is crucial to choose ICSI carefully, and conventional IVF continues to be a significant option.[47]

3.4.3 Risk of OHSS and prevention strategies

Ovarian hyperstimulation syndrome (OHSS) is a serious IVF complication caused by enlarged, overly responsive ovaries, leading to fluid shifts, dehydration, and increased clot risk. Severe OHSS can be life-threatening, and its incidence is hard to determine due to variable reporting. GnRH antagonist protocols have been shown to reduce the risk of OHSS. The syndrome is more severe and prolonged in cases of pregnancy or following hCG exposure. Mild to moderate OHSS is often managed outpatient, while severe cases require hospitalization, highlighting the need for preventive and evidence-based strategies.[48]

4. FUTURE DIRECTION

4.1 Precision Medicines and Genomics

Polycystic ovary syndrome (PCOS) is a common endocrine–metabolic disorder in women of reproductive age, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Its clinical features range from reproductive abnormalities to metabolic complications like insulin resistance, obesity, and cardiovascular risk.[49] This heterogeneity reflects complex genetic, epigenetic, and environmental interactions. PCOS is therefore an

ideal candidate for precision medicine, tailoring diagnosis and treatment to individual genetic and phenotypic profiles.[50]

4.1.1. Genetic Risk Factors in PCOS

Polygenic nature and heritability: PCOS shows strong familial aggregation, with first-degree relatives having higher prevalence of PCOS and related metabolic traits, and twin studies indicate moderate to high heritability. It is a polygenic disorder influenced by multiple common genetic variants rather than following simple Mendelian inheritance.[51]

Genome-wide association studies (GWAS): Genome-wide association studies (GWAS) have identified PCOS susceptibility loci such as DENND1A, THADA, LHCGR, FSHR, and INSR, affecting steroidogenesis, gonadotropin signaling, insulin resistance, and energy metabolism.[52,53,54] DENND1A.V2 enhances androgen production in theca cells, linking genetics to hyperandrogenism.[55] LHCGR and FSHR variants influence hypothalamic–pituitary–ovarian axis regulation and ovulatory function.[53,56] INSR and THADA variants highlight the genetic overlap between PCOS and metabolic disorders like type 2 diabetes.[52]

Polygenic risk scores and population differences: Polygenic risk scores (PRS) from GWAS variants can help stratify PCOS risk and relate to features like hyperandrogenism and menstrual irregularity. However, their clinical utility is limited by modest predictive accuracy and lower performance across ethnic groups. Most GWAS data come from European and East Asian populations, highlighting the need for broader ancestral representation.[54,57]

Clinical implications: Although genetic discoveries have substantially advanced understanding of PCOS biology, translation into routine clinical practice remains limited. At present, genetic testing is not routinely recommended for PCOS diagnosis, but ongoing integration of functional genomics, single-cell transcriptomics, and epigenomics may enable future genotype-informed therapeutic strategies.[50,58]

4.1.2. Epigenetic Signatures in PCOS

Role of epigenetics in disease pathogenesis: Epigenetic mechanisms including DNA methylation, histone modifications, and non-coding RNAs play a crucial role in regulating gene expression without altering the underlying DNA sequence. In PCOS, epigenetic dysregulation provides a mechanistic link between genetic susceptibility and environmental

exposures such as prenatal androgen excess, obesity, diet, and endocrine-disrupting chemicals.[59]

DNA methylation changes: Multiple studies have reported altered DNA methylation patterns in ovarian tissue, adipose tissue, skeletal muscle, and peripheral blood from women with PCOS. Differential methylation has been observed in genes involved in steroidogenesis (e.g., CYP11A1, CYP17A1, CYP19A1), insulin signaling (INSR, IRS1), inflammation, and follicular development.[59,60,61] Importantly, some of these methylation changes correlate with altered gene expression, suggesting functional relevance rather than epiphenomena.

Non-coding RNAs and chromatin regulation: MicroRNAs (miRNAs) influence androgen synthesis, insulin resistance, and granulosa cell proliferation in PCOS, and circulating miRNAs serve as promising non-invasive biomarkers.[62] Chromatin-mapping studies show many PCOS-associated variants lie in regulatory regions, supporting a regulatory mechanism for genetic risk.[58]

Epigenetic plasticity and therapeutic relevance: A defining feature of epigenetic modifications is their reversibility. Lifestyle interventions such as weight loss, exercise, and dietary modification have been shown to partially normalize aberrant epigenetic profiles in women with PCOS. This plasticity highlights the potential utility of epigenetic markers both as indicators of treatment response and as future therapeutic targets. Nevertheless, heterogeneity in study design, tissue specificity, and analytical methods currently limits reproducibility and clinical translation.[60,63]

4.1.3. Individualized Therapy Based on Phenotype

Rationale for phenotype-driven management: The heterogeneity of PCOS necessitates individualized treatment strategies rather than a uniform therapeutic approach. Traditional classifications, such as the Rotterdam phenotypes, and newer data-driven clustering methods reveal distinct subtypes characterized by varying degrees of hyperandrogenism, metabolic dysfunction, and reproductive impairment. These phenotypes differ in prognosis, fertility outcomes, and long-term metabolic risk, supporting the need for personalized management.[64]

Precision medicine approach to treatment: In metabolic-dominant PCOS, lifestyle interventions are key, with GLP-1 receptor agonists showing promise for weight loss,

improved insulin sensitivity, and potentially better menstrual and ovulatory function.[65-67] For reproductive-dominant PCOS, ovulation induction with letrozole remains first-line, with future personalization possible using genetic markers and AMH.[56,64] Hyperandrogenic PCOS is managed with oral contraceptives and anti-androgens. Molecular advances may allow targeted therapies for specific genetic subgroups.[55,58]

Integration of multi-omics and artificial intelligence: Integration of genomics, epigenomics, transcriptomics, and metabolomics using artificial intelligence and machine-learning models has led to the identification of biologically meaningful PCOS subtypes. These approaches show promise for predicting treatment response and long-term risks such as type 2 diabetes and cardiovascular disease. However, prospective validation, cost-effectiveness evaluation, and ethical considerations must be addressed before routine clinical implementation.[57,64]

4.2 Role of Artificial Intelligence in PCOS

4.2.1 AI-Assisted Diagnosis

Artificial intelligence (AI) enhances PCOS diagnosis by reducing variability in symptom, lab, and ultrasound interpretation. Machine learning algorithms, such as random forests and support vector machines, analyze clinical data to differentiate PCOS from non-PCOS with high accuracy.[65,68,69] Deep learning, especially convolutional neural networks, automates ovarian ultrasound analysis, identifying polycystic morphology and counting follicles with over 90% sensitivity and specificity.[67,70,73] Explainable AI (XAI) methods like SHAP and LIME improve transparency by highlighting features influencing predictions.[71] These tools reduce operator dependence and improve consistency in imaging interpretation. Overall, AI provides reproducible, high-precision support for reliable PCOS diagnosis.

4.2.2 Risk Prediction Models

AI-driven models can predict PCOS risk and related metabolic and reproductive complications by analyzing demographic, clinical, biochemical, and lifestyle data, stratifying patients more precisely than traditional methods.[68,69] These models are integrated into mHealth platforms, allowing self-assessment and early screening with strong predictive performance.[72] Multi-omics AI frameworks combining genetic, epigenomic, and metabolomic data show promise for improved accuracy. Larger, multi-ethnic datasets and external validation are needed before widespread clinical use.[65,75]

4.2.3 Personalized Treatment Planning

AI helps optimize PCOS treatment by predicting individual responses to therapies using clinical, metabolic, menstrual, ovarian, and lifestyle data. Machine learning models guide ovulation-induction agent selection and gonadotropin dosing in ART, reducing risks like ovarian hyperstimulation.[68,74] In metabolic management, AI identifies patients likely to benefit from lifestyle changes, metformin, or GLP-1 agonists by analyzing weight, insulin resistance, diet, and hormones. These tools personalize therapy to improve both metabolic and reproductive outcomes.[65,74] Future applications include adaptive reinforcement learning systems and digital twins to simulate treatment outcomes.[71,75]

4.3 Gaps in Current Research & Challenges

Despite significant advances in understanding the pathophysiology of polycystic ovary syndrome (PCOS), several critical gaps persist in research and clinical practice. These challenges hinder accurate diagnosis, long-term disease management, and the development of individualized therapeutic strategies.

4.3.1 Inconsistent Diagnostic Criteria

A major challenge in PCOS research is the lack of uniform diagnostic criteria, with NIH, Rotterdam, and Androgen Excess and PCOS Society guidelines emphasizing different features.[76,77] The Rotterdam criteria allow diagnosis with any two of three features, resulting in diverse phenotypes under one label and complicating research comparisons. Variations in ultrasound technology, follicle count thresholds, and androgen assays add further diagnostic inconsistency.[76] Clinician awareness and adherence to standardized guidelines are often limited, especially among non-specialists. These issues underscore the need for globally harmonized diagnostic standards and improved clinician education.[77]

4.3.2 Lack of Long-Term Outcome Data

A critical gap in PCOS research is the lack of long-term, prospective data, as most studies are cross-sectional or short-term and do not capture its chronic nature. This limits understanding of PCOS's long-term effects on metabolic, cardiovascular, reproductive, and mental health.[78,79] The sustained efficacy and safety of treatments like metformin, hormonal contraceptives, and lifestyle interventions remain unclear.[78] Large-scale, longitudinal studies are needed to assess long-term outcomes, emerging therapies, and potential transgenerational effects.[79]

4.3.3 Need for More Phenotype-Specific Treatments

PCOS is a heterogeneous disorder with reproductive, metabolic, and psychological manifestations, yet current treatments are largely symptom-based.[80] Proposed phenotypes based on hyperandrogenism, ovulatory dysfunction, and ovarian morphology have limited evidence linking them to treatment response or prognosis. Heterogeneous patient populations in trials may obscure benefits for specific subgroups.[80,81] Future research should integrate phenotypic, molecular, metabolic, and genetic data to enable personalized treatment and improve outcomes.[81]

5. CONCLUSION

Polycystic ovary syndrome (PCOS) is a common, heterogeneous endocrine disorder with reproductive, metabolic, and psychological effects, complicated by variable clinical presentation and differing diagnostic criteria such as NIH, Rotterdam, and AE-PCOS guidelines. Advances in hormonal assays, imaging, and biomarkers have improved diagnosis, though challenges remain, especially in adolescents and diverse populations. Management focuses on a holistic, patient-centered approach, with lifestyle modification as the cornerstone and pharmacological therapies tailored to symptoms and fertility goals. Complementary therapies and assisted reproductive technologies further support infertility management. Future directions emphasize precision medicine using genetic, epigenetic, and phenotypic data to personalize care. AI also shows promise in improving diagnostic consistency, risk prediction, and therapy selection, though gaps in long-term data and phenotype-specific trials persist.[82]

6. REFERENCE

1. Williams, T., Mortada, R., & Porter, S. (2016). Diagnosis and treatment of polycystic ovary syndrome. *American family physician*, *94*(2): 106-113.
2. Hoeger, K. M., Dokras, A., & Piltonen, T. (2021). Update on PCOS: consequences, challenges, and guiding treatment. *The Journal of Clinical Endocrinology & Metabolism*, *106*(3): e1071-e1083.
3. Legro, R. S., Arslanian, S. A., Ehrmann, D. A., Hoeger, K. M., Murad, M. H., Pasquali, R., & Welt, C. K. (2013). Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, *98*(12): 4565-4592.

4. Artini, P. G., Di Berardino, O. M., Simi, G., Papini, F., Ruggiero, M., Monteleone, P., & Cela, V. (2010). Best methods for identification and treatment of PCOS. *Minerva ginecologica*, *62*(1): 33.
5. Harwood, K., Vuguin, P., & DiMartino-Nardi, J. (2007). Current approaches to the diagnosis and treatment of polycystic ovarian syndrome in youth. *Hormone Research in Paediatrics*, *68*(5): 209-217.
6. Meczekalski, B., Niwczyk, O., Kostrzak, A., Maciejewska-Jeske, M., Bala, G., & Szeliga, A. (2023). PCOS in Adolescents—Ongoing riddles in diagnosis and treatment. *Journal of clinical medicine*, *12*(3): 1221.
7. Sheehan, M. T. (2004). Polycystic ovarian syndrome: diagnosis and management. *Clinical medicine & research*, *2*(1): 13-27.
8. Legro, R. (2015). Diagnosis and treatment of polycystic ovary syndrome (PCOS): An interview with Richard Legro. *BMC medicine*, *13*(1): 64.
9. Hadidi, M., Karimabadi, K., Ghanbari, E., Rezakhani, L., & Khazaei, M. (2023). Stem cells and exosomes: as biological agents in the diagnosis and treatment of polycystic ovary syndrome (PCOS). *Frontiers in endocrinology*, *14*, 1269266.
10. Islam, H., Masud, J., Islam, Y. N., & Haque, F. K. M. (2022). An update on polycystic ovary syndrome: A review of the current state of knowledge in diagnosis, genetic etiology, and emerging treatment options. *Women's Health*, *18*: 17455057221117966.
11. Akhter, N., Sana, S., Anjum, F., Tariq, M., Afzaal, M., Siddique, Z., & Sana, A. (2025). The Role of Imaging and Biochemistry in the Diagnosis and Management of Polycystic Ovary Syndrome (PCOS). *Understanding Polycystic Ovary Syndrome-Symptoms, Diagnosis, and Treatment Options: Symptoms, Diagnosis, and Treatment Options*, 107.
12. Moka, M. K., Sriram, D. K., & George, M. (2025). Recent advances in individualized clinical strategies for polycystic ovary syndrome: Evidence from clinical trials and emerging pharmacotherapies. *Clinical Therapeutics*, *47*(2): 158–167. https://doi.org/10.1016/j.clinthera.2024.11.015
13. Cowan, S., Lim, S., Alycia, C., Pirotta, S., Thomson, R., Gibson-Helm, M., Blackmore, R., Naderpoor, N., Bennett, C., Ee, C., Rao, V., Mousa, A., Alesi, S., & Moran, L. (2023). Lifestyle management in polycystic ovary syndrome - beyond diet and physical activity. *BMC Endocrine Disorders*, *23*(1): 14. https://doi.org/10.1186/s12902-022-01208-y

14. Ornstein, R. M., Copperman, N. M., & Jacobson, M. S. (2011). Effect of weight loss on menstrual function in adolescents with polycystic ovary syndrome. *Journal of Pediatric and Adolescent Gynecology*, *24*(3): 161–165. https://doi.org/10.1016/j.jpag.2011.01.002
15. Tolino, A., Gambardella, V., Caccavale, C., D'Ettore, A., Giannotti, F., D'Antò, V., & De Falco, C. L. (2005). Evaluation of ovarian functionality after a dietary treatment in obese women with polycystic ovary syndrome. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *119*(1): 87–93. https://doi.org/10.1016/j.ejogrb.2004.06.043
16. Huber-Buchholz, M. M., Carey, D. G., & Norman, R. J. (1999). Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. *The Journal of Clinical Endocrinology and Metabolism*, *84*(4): 1470–1474. https://doi.org/10.1210/jcem.84.4.5596
17. Pasquali, R., Gambineri, A., Cavazza, C., Ibarra Gasparini, D., Ciampaglia, W., Cognigni, G. E., & Pagotto, U. (2011). Heterogeneity in the responsiveness to long-term lifestyle intervention and predictability in obese women with polycystic ovary syndrome. *European Journal of Endocrinology*, *164*(1): 53–60. https://doi.org/10.1530/EJE-10-0692
18. Teede, H. J., Tay, C. T., Laven, J., Dokras, A., Moran, L. J., Piltonen, T. T., Costello, M. F., Boivin, J., Redman, L. M., Boyle, J. A., Norman, R. J., Mousa, A., Joham, A. E., & International PCOS Network. (2023). Recommendations from the 2023 International Evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Human Reproduction (Oxford, England)*, *38*(9): 1655–1679. https://doi.org/10.1093/humrep/dead156
19. Hadi, A., Roger, A., Pierson, M. E., & Lujan, G. A. (n.d.). *Effects of Dietary Glycemic Index and Glycemic Load on Cardiometabolic and Reproductive Profiles in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis of Randomized Controlled Trials Author links open overlay panelMaryam Kazemi*.
20. Zhang, X., Zheng, Y., Guo, Y., & Lai, Z. (2019). The effect of low carbohydrate diet on polycystic ovary syndrome: A meta-analysis of randomized controlled trials. *International Journal of Endocrinology*, *2019*; 4386401. https://doi.org/10.1155/2019/4386401
21. Info, N. (Ed.). (n.d.). *Relation of nutrients and hormones in polycystic ovary syndrome2 Sidika E Kasim-Karakas sekarakas@ucdavis*.
22. Katcher, H. I., Kunselman, A. R., Dmitrovic, R., Demers, L. M., Gnatuk, C. L., Kris-Etherton, P. M., & Legro, R. S. (2009). Comparison of hormonal and metabolic markers

after a high-fat, Western meal versus a low-fat, high-fiber meal in women with polycystic ovary syndrome. *Fertility and Sterility*, *91*(4): 1175–1182. https://doi.org/10.1016/j.fertnstert.2008.01.035

23. *Pharmacological and Non-Pharmacological Interventions for Polycystic Ovary Syndrome (PCOS) in Indian Women: A Systematic Review and Meta-Analysis*. (n.d.).
24. Scarpello, J. H. B., & Howlett, H. C. S. (2008). Metformin therapy and clinical uses. *Diabetes & Vascular Disease Research: Official Journal of the International Society of Diabetes and Vascular Disease*, *5*(3): 157–167. https://doi.org/10.3132/dvdr.2008.027
25. Nandikola, J. R., Rangnath Wayal, S., Vijayabanu, Ravindra, Keshava, Chatterjee, A., Jaganmohan, C., R. Bhise, M., & Devarakonda, S. (2025). Antidiabetic management strategies for treatment of polycystic ovarian syndrome. *Journal of Neonatal Surgery*, *14*(1S): 192–209. https://doi.org/10.52783/jns.v14.1517
26. Dutta, S., Sengupta, P., Rao, S., Elgarawany, G. E., Samrot, A. V., Rosas, I. M., & Roychoudhury, S. (2025). Targeting polycystic ovary syndrome (PCOS) pathophysiology with flavonoids: From adipokine-cytokine crosstalk to insulin resistance and reproductive dysfunctions. *Pharmaceuticals (Basel, Switzerland)*, *18*(10), 1575. https://doi.org/10.3390/ph18101575
27. Singh, S., Pal, N., Shubham, S., Sarma, D. K., Verma, V., Marotta, F., & Kumar, M. (2023). Polycystic ovary syndrome: Etiology, current management, and future therapeutics. *Journal of Clinical Medicine*, *12*(4): 1454. https://doi.org/10.3390/jcm12041454
28. Abdalla, M. A., Deshmukh, H., Atkin, S., & Sathyapalan, T. (2020). A review of therapeutic options for managing the metabolic aspects of polycystic ovary syndrome. *Therapeutic Advances in Endocrinology and Metabolism*, *11*, 2042018820938305. https://doi.org/10.1177/2042018820938305
29. Rashid, R., Mir, S. A., Kareem, O., Ali, T., Ara, R., Malik, A., Amin, F., & Bader, G. N. (2022). Polycystic ovarian syndrome-current pharmacotherapy and clinical implications. *Taiwanese Journal of Obstetrics & Gynecology*, *61*(1): 40–50. https://doi.org/10.1016/j.tjog.2021.11.009
30. Madnani, N., Khan, K., Chauhan, P., & Parmar, G. (2013). Polycystic ovarian syndrome. *Indian Journal of Dermatology, Venereology and Leprology*, *79*(3): 310–321. https://doi.org/10.4103/0378-6323.110759

31. Martin, K. A., Chang, R. J., Ehrmann, D. A., Ibanez, L., Lobo, R. A., Rosenfield, R. L., Shapiro, J., Montori, V. M., & Swiglo, B. A. (2008). Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*, *93*(4): 1105–1120. https://doi.org/10.1210/jc.2007-2437
32. The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. (2008). Consensus on infertility treatment related to polycystic ovary syndrome. *Human Reproduction (Oxford, England)*, *23*(6): 1474–1474. https://doi.org/10.1093/humrep/den199
33. Carroll, N., & Palmer, J. R. (2001). A comparison of intrauterine versus intracervical insemination in fertile single women. *Fertility and Sterility*, *75*(4): 656–660. https://doi.org/10.1016/s0015-0282(00)01782-9
34. Cefalu, W. T. (2010). The physiologic role of incretin hormones: clinical applications. *The Journal of the American Osteopathic Association*, *110*(3 Suppl 2): S8–S14.
35. Yaribeygi, H., Sathyapalan, T., & Sahebkar, A. (2019). Molecular mechanisms by which GLP-1 RA and DPP-4i induce insulin sensitivity. *Life Sciences*, *234*(116776): 116776. https://doi.org/10.1016/j.lfs.2019.116776
36. Izquierdo, D., Foyouzi, N., Kwintkiewicz, J., & Duleba, A. J. (2004). Mevastatin inhibits ovarian theca-interstitial cell proliferation and steroidogenesis. *Fertility and Sterility*, *82 Suppl, 3*: 1193–1197. https://doi.org/10.1016/j.fertnstert.2004.03.037
37. Chen, J., Huang, C., Zhang, T., Gong, W., Deng, X., Liu, H., Liu, J., & Guo, Y. (2021). The effects of statins on hyperandrogenism in women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Reproductive Biology and Endocrinology: RB&E*, *19*(1): 189. https://doi.org/10.1186/s12958-021-00863-5
38. Lin, M.-W., & Wu, M.-H. (2015). The role of vitamin D in polycystic ovary syndrome. *The Indian Journal of Medical Research*, *142*(3): 238–240. https://doi.org/10.4103/0971-5916.166527
39. Kwon, C.-Y., Cho, I.-H., & Park, K. S. (2020). Therapeutic effects and mechanisms of herbal medicines for treating polycystic ovary syndrome: A review. *Frontiers in Pharmacology*, *11:* 1192. https://doi.org/10.3389/fphar.2020.01192
40. Muhammed Saeed, A. A., Noreen, S., Awlqadr, F. H., Farooq, M. I., Qadeer, M., Rai, N., Farag, H. A., & Saeed, M. N. (2025). Nutritional and herbal interventions for polycystic

ovary syndrome (PCOS): a comprehensive review of dietary approaches, macronutrient impact, and herbal medicine in management. *Journal of Health, Population, and Nutrition*, *44*(1): 143. https://doi.org/10.1186/s41043-025-00899-y

41. Fisher, J. R. W., & Hammarberg, K. (2012). Psychological and social aspects of infertility in men: an overview of the evidence and implications for psychologically informed clinical care and future research. *Asian Journal of Andrology*, *14*(1): 121–129. https://doi.org/10.1038/aja.2011.72
42. Sciorio, R., & Esteves, S. C. (2020). Clinical utility of freeze-all approach in ART treatment: A mini-review. *Cryobiology*, *92*: 9–14. https://doi.org/10.1016/j.cryobiol.2019.11.041
43. Hussain, A., Abbas, M., Zain-ul-Abideen, Mustafa, G., Lateef, M., Mansoor, A., Raza, Y., Hayat, A., & Lashari, M. H. (2025). Innovations and challenges in modern infertility treatment: bridging technology and psychosocial care. *Middle East Fertility Society Journal*, *30*(1). https://doi.org/10.1186/s43043-025-00257-2
44. Costello, M. F., Misso, M. L., Balen, A., Boyle, J., Devoto, L., Garad, R. M., Hart, R., Johnson, L., Jordan, C., Legro, R. S., Norman, R. J., Mocanu, E., Qiao, J., Rodgers, R. J., Rombauts, L., Tassone, E. C., Thangaratinam, S., Vanky, E., Teede, H. J., & International PCOS Network. (2019). Evidence summaries and recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome: assessment and treatment of infertility. *Human Reproduction Open*, *2019;* 1: hoy021. https://doi.org/10.1093/hropen/hoy021
45. Mercorio, A., Della Corte, L., De Angelis, M. C., Buonfantino, C., Ronsini, C., Bifulco, G., &,Giampaolino, P. (2022). Ovarian drilling: Back to the future. *Medicina (Kaunas, Lithuania)*, *58*(8): 1002. https://doi.org/10.3390/medicina58081002
46. Liang, Y., Zhang, Q., & Lou, Z. (2025). Effect of pre-treatment with oral short-acting contraceptives on assisted reproductive technology outcomes in patients with polycystic ovary syndrome: a meta-analysis. *Frontiers in Endocrinology*, *16:* 1545508. https://doi.org/10.3389/fendo.2025.1545508
47. Balli, M., Cecchele, A., Pisaturo, V., Makieva, S., Carullo, G., Somigliana, E., Paffoni, A., & Vigano',P. (2022). Opportunities and limits of conventional IVF versus ICSI: It is time to come off the fence. *Journal of Clinical Medicine*, *11*(19): 5722. https://doi.org/10.3390/jcm11195722
48. Tsampras, N., Palinska-Rudzka, K., Alebrahim, Y., Craciunas, L., & Mathur, R. (2025). Prevention of ovarian hyperstimulation syndrome (OHSS): British Fertility Society policy

and practice guideline. *Human Fertility (Cambridge, England)*, *28*(1): 2441827. https://doi.org/10.1080/14647273.2024.2441827

49. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ; International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril, 2018 Aug; 110(3): 364-379. Doi:10.1016/j.fertnstert.2018.05.004. Epub 2018 Jul 19. PMID: 30033227; PMCID: PMC6939856.
50. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod, 2004 Jan; 19(1): 41-7. Doi: 10.1093/humrep/deh098. PMID: 14688154.
51. Day F, Karaderi T, Jones MR, Meun C, He C, Drong A, Kraft P, Lin N, Huang H, Broer L, Magi R, Saxena R, Laisk T, Urbanek M, Hayes MG, Thorleifsson G, Fernandez-Tajes J, Mahajan A, Mullin BH, Stuckey BGA, Spector TD, Wilson SG, Goodarzi MO, Davis L, Obermayer-Pietsch B, Uitterlinden AG, Anttila V, Neale BM, Jarvelin MR, Fauser B, Kowalska I, Visser JA, Andersen M, Ong K, Stener-Victorin E, Ehrmann D, Legro RS, Salumets A, McCarthy MI, Morin-Papunen L, Thorsteinsdottir U, Stefansson K; 23andMe Research Team; Styrkarsdottir U, Perry JRB, Dunaif A, Laven J, Franks S, Lindgren CM, Welt CK. Large-scale genome-wide meta-analysis of polycystic ovary syndrome suggests shared genetic architecture for different diagnosis criteria. PLoS Genet, 2018 Dec 19; 14(12): e1007813. Doi: 10.1371/journal.pgen.1007813. Erratum in: PLoS Genet, 2019 Dec 5; 15(12): e1008517. Doi: 10.1371/journal.pgen.1008517. PMID: 30566500; PMCID: PMC6300389.
52. McAllister, J. M., Modi, B., Miller, B. A., Biegler, J., Bruggeman, R., Legro, R. S., & Strauss, J. F. (2014). Overexpression of a DENND1A isoform produces a polycystic ovary syndrome theca phenotype. Proceedings of the National Academy of Sciences, 111(15): E1519-27. https://doi.org/10.1073/pnas.1400574111
53. Waterbury JS, Teves ME, Gaynor A, Han AX, Mavodza G, Newell J, Strauss JF 3rd, McAllister JM. The PCOS GWAS Candidate Gene ZNF217 Influences Theca Cell Expression of DENND1A.V2, CYP17A1, and Androgen Production. J Endocr Soc, 2022 May 13; 6(7): bvac078. Doi: 10.1210/jendso/bvac078. PMID: 35668995; PMCID: PMC9155636.
54. Cao P, Yang W, Wang P, Li X, Nashun B. Characterization of DNA Methylation and Screening of Epigenetic Markers in Polycystic Ovary Syndrome. Front Cell Dev Biol,

2021 May 25; 9: 664843. Doi: 10.3389/fcell.2021.664843. PMID: 34113617; PMCID: PMC8186667.

55. Udesen PB, Sørensen AE, Svendsen R, Frisk NLS, Hess AL, Aziz M, Wissing MLM, Englund ALM, Dalgaard LT. Circulating miRNAs in Women with Polycystic Ovary Syndrome: A Longitudinal Cohort Study. Cells, 2023 Mar 23; 12(7): 983. Doi: 10.3390/cells12070983. PMID: 37048055; PMCID: PMC10093401.
56. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, Christman GM, Huang H, Yan Q, Alvero R, Haisenleder DJ, Barnhart KT, Bates GW, Usadi R, Lucidi S, Baker V, Trussell JC, Krawetz SA, Snyder P, Ohl D, Santoro N, Eisenberg E, Zhang H; NICHD Reproductive Medicine Network. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med, 2014 Jul 10; 371(2): 119-29. Doi: 10.1056/NEJMoa1313517. Erratum in: N Engl J Med, 2014 Oct 9; 317(15): 1465. PMID: 25006718; PMCID: PMC4175743.
57. Hudanich M, Smith SN, Marino A, Riskin SI. The Effects of Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists on Polycystic Ovarian Syndrome: A Scoping Review. Cureus, 2025 Sep 24; 17(9): e93104. Doi: 10.7759/cureus.93104. PMID: 41141001; PMCID: PMC12551431.
58. Austregésilo de Athayde De Hollanda Morais B, Martins Prizão V, de Moura de Souza M, Ximenes Mendes B, Rodrigues Defante ML, Cosendey Martins O, Rodrigues AM. The efficacy and safety of GLP-1 agonists in PCOS women living with obesity in promoting weight loss and hormonal regulation: A meta-analysis of randomized controlled trials. J Diabetes Complications, 2024 Oct; 38(10): 108834. Doi: 10.1016/j.jdiacomp.2024.108834. Epub 2024 Aug 20. PMID: 39178623.
59. Priya Sharma, Amit Singh, Shweta Daryani, Tulsi Brahma, Balpreet Kaur, Preeti Khetarpal,Genome-wide DNA methylation analysis in blood identifies differentially methylated regions related to polycystic ovary syndrome, Gene Reports, 2024; 35:. 101927ISSN 2452-0144, https://doi.org/10.1016/j.genrep.2024.101927. (https://www.sciencedirect.com/science/article/pii/S2452014424000505)
60. Reuters Health News. Weight-loss drugs fill a treatment gap for women with hormone disorder PCOS, doctors say, 2025 Dec 9. (report summarizing growing GLP-1 use among PCOS patients and gaps in dedicated trials).
61. Smet ME, McLennan A. Rotterdam criteria, the end. Australas J Ultrasound Med, 2018 May 17; 21(2): 59-60. Doi: 10.1002/ajum.12096. PMID: 34760503; PMCID: PMC8409808.

62. Censin JC, Bovijn J, Holmes MV, Lindgren CM. Colocalization analysis of polycystic ovary syndrome to identify potential disease-mediating genes and proteins. Eur J Hum Genet, 2021 Sep; 29(9): 1446-1454. doi: 10.1038/s41431-021-00835-8. Epub 2021 Mar 4. PMID: 33664499; PMCID: PMC8440598.
63. Hadi S, Khoshraftar SH, Kiani Darabi AH, Soleimani A, Nejabati HR. Extracellular fluid miRNAs in PCOS. Clin Chim Acta, 2025 Aug 15; 576: 120404. Doi: 10.1016/j.cca.2025.120404. Epub 2025 May 28. PMID: 40446894.
64. Wasim T, Nasrin T, Zunair J, Irshad S. Efficacy of Letrozole vs Clomiphene Citrate for induction of ovulation in women with polycystic ovarian syndrome. Pak J Med Sci, 2024 Jan-Feb; 40(1Part-I): 78-83. Doi: 10.12669/pjms.40.1.7971. PMID: 38196458; PMCID: PMC10772410.
65. Ghaderzadeh M, Garavand A, Salehnasab C. Artificial intelligence in polycystic ovary syndrome: a systematic review of diagnostic and predictive applications. BMC Med Inform Decis Mak, 2025 Nov 24; 25(1): 427. Doi: 10.1186/s12911-025-03255-6. PMID: 41286838; PMCID: PMC12642037.
66. Wang J, Chen R, Long H, He J, Tang M, Su M, Deng R, Chen Y, Ni R, Zhao S, Rao M, Wang H, Tang L. Artificial intelligence in polycystic ovarian syndrome management: past, present, and future. Radiol Med, 2025 Sep; 130(9): 1409-1441. Doi: 10.1007/s11547-025-02032-9. Epub 2025 Jun 23. PMID: 40549330; PMCID: PMC12454626.
67. Zhao B, Wen L, Huang Y, Fu Y, Zhou S, Liu J, Liu M, Li Y. A Deep Learning-Based Automatic Recognition Model for Polycystic Ovary Ultrasound Images. Balkan Med J., 2025 Sep 1; 42(5): 419-428. Doi: 10.4274/balkanmedj.galenos.2025.2025-5-114. Epub 2025 Aug 11. PMID: 40785235; PMCID: PMC12402960.
68. Agirsoy, M., & Oehlschlaeger, M. A. (2025). A machine learning approach for non-invasive PCOS diagnosis from ultrasound and clinical features. Scientific Reports, 15(1): 33638. https://doi.org/10.1038/s41598-025-10453-9
69. Zad Z, Jiang VS, Wolf AT, Wang T, Cheng JJ, Paschalidis IC, Mahalingaiah S. Predicting polycystic ovary syndrome with machine learning algorithms from electronic health records. Front Endocrinol (Lausanne), 2024 Jan 30; 15: 1298628. Doi: 10.3389/fendo.2024.1298628. PMID: 38356959; PMCID: PMC10866556.
70. S S, Umapathy S, Alhajlah O, Almutairi F, Aslam S, R K A. F-Net: Follicles Net an efficient tool for the diagnosis of polycystic ovarian syndrome using deep learning

techniques. PLoS One, 2024 Aug 15; 19(8): e0307571. doi: 10.1371/journal.pone.0307571. PMID: 39146307; PMCID: PMC11326594

71. Elmannai, H., El-Rashidy, N., Mashal, I., Alohali, M. A., Farag, S., El-Sappagh, S., & Saleh, H. (2023). Polycystic ovary syndrome detection machine learning model based on optimized feature selection and explainable artificial intelligence. Diagnostics, 13(8): 1506. https://doi.org/10.3390/diagnostics13081506
72. Zigarelli, A., Jia, Z., & Lee, H. (2022). Machine-Aided Self-diagnostic prediction models for polycystic ovary Syndrome: Observational study. *JMIR Formative Research*, *6*(3): e29967. https://doi.org/10.2196/29967
73. Alamoudi, A., Khan, I. U., Aslam, N., Alqahtani, N., Alsaif, H. S., Dandan, O. A., Gadeeb, M. A., & Bahrani, R. A. (2023). A deep learning fusion approach to diagnosis the polycystic ovary syndrome (PCOS). *Applied Computational Intelligence and Soft Computing*, *2023*, 1–15. https://doi.org/10.1155/2023/9686697
74. Panjwani, B., Yadav, J., Mohan, V., Agarwal, N., & Agarwal, S. (2025). Optimized machine learning for the early detection of polycystic ovary syndrome in women. *Sensors*, *25*(4): 1166. https://doi.org/10.3390/s25041166
75. Wang J, Chen R, Long H, He J, Tang M, Su M, Deng R, Chen Y, Ni R, Zhao S, Rao M, Wang H, Tang L. Artificial intelligence in polycystic ovarian syndrome management: past, present, and future. Radiol Med, 2025 Sep; 130(9): 1409-1441. doi: 10.1007/s11547-025-02032-9. Epub 2025 Jun 23. PMID: 40549330; PMCID: PMC12454626.
76. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ; International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril, 2018 Aug; 110(3): 364379. Doi:10.1016/j.fertnstert.2018.05.004. Epub 2018 Jul 19. PMID: 30033227; PMCID: PMC6939856.
77. Dokras A, Saini S, Gibson-Helm M, Schulkin J, Cooney L, Teede H. Gaps in knowledge among physicians regarding diagnostic criteria and management of polycystic ovary syndrome. Fertil Steril, 2017 Jun; 107(6): 1380-1386.e1. doi: 10.1016/j.fertnstert.2017.04.011. Epub 2017 May 5. PMID: 28483503.
78. Palomba S, Santagni S, Falbo A, La Sala GB. Complications and challenges associated with polycystic ovary syndrome: current perspectives. Int J Womens Health, 2015 Jul 31; 7: 745-63. Doi:10.2147/IJWH.S70314. PMID: 26261426; PMCID: PMC4527566.

79. Vasudevan, S., Gautam, R., Maan, P., Arora, A., Ganie, A., Jabbar, P. K., & Arora, T. (2025). A sustainable public health framework for PCOS management in low- and middle-income countries: a narrative review. Frontiers in Reproductive Health, 7: 1627670. https://doi.org/10.3389/frph.2025.1627670
80. Azziz R, Carmina E, Chen Z, Dunaif A, Laven JS, Legro RS, Lizneva D, Natterson-Horowtiz B, Teede HJ, Yildiz BO. Polycystic ovary syndrome. Nat Rev Dis Primers, 2016 Aug 11; 2: 16057. Doi: 10.1038/nrdp.2016.57. PMID: 27510637.
81. Hoeger KM, Dokras A, Piltonen T. Update on PCOS: Consequences, Challenges, and Guiding Treatment. J Clin Endocrinol Metab, 2021 Mar 8; 106(3): e1071-e1083. Doi: 10.1210/clinem/dgaa839. PMID: 33211867.
82. Rudraksh PK Chavda, Bhavya P Patel, Kachhadiya Hemanshi, Patel Nirali, Dr. Ashok Choudhary, Dr. Divyakant Patel, Pregnancy Complications and Outcomes in Women with Polycystic Ovary Syndrome: An Updated Review, Int. J. of Pharm.Sci., 2025; 3(10): 1696-1709. https://doi.org/10.5281/zenodo.17369994