Polycystic Ovary Syndrome: Etiology, Current Management, and Future Therapeutics

Jagruti Santosh Patil, Siddhesh Deokar, Janhavi Patil,
Jaydeep Patil, Pranjali Pralhad Parit
Final Year B Pharm Students
Matoshri College of Pharmacy,Eklahare,Nashik

1. Abstract

Polycystic Ovary Syndrome (PCOS) is one of the most prevalent and complex endocrine and metabolic disorders affecting women of reproductive age. Characterized by chronic anovulation, hyperandrogenism, and polycystic ovarian morphology, PCOS manifests through a wide range of clinical, hormonal, and metabolic abnormalities. The etiology of PCOS is multifactorial, involving intricate interactions between genetic predisposition, hormonal imbalance, insulin resistance, inflammation, and environmental influences such as diet and lifestyle. These interconnected factors disrupt ovarian folliculogenesis, leading to menstrual irregularities, infertility, and metabolic disturbances including obesity and type 2 diabetes.

Current management of PCOS primarily focuses on symptom control, hormonal regulation, and metabolic correction. Lifestyle modification remains the cornerstone of therapy, complemented by pharmacological interventions such as insulin sensitizers (Metformin), ovulation induction agents (Letrozole and Clomiphene Citrate), oral contraceptives, and anti-androgenic drugs. Surgical procedures like laparoscopic ovarian drilling are considered in resistant cases. However, treatment strategies must be individualized based on patient phenotype, reproductive goals, and metabolic risk factors.

Recent advancements in PCOS research emphasize the integration of molecular biology, nanotechnology, and personalized medicine to improve therapeutic efficacy. Emerging therapies including inositol isomers, nutraceuticals, probiotics, and gene-targeted approaches show promising results in restoring hormonal balance and metabolic homeostasis. The exploration of gut microbiota modulation and nanoformulation-based drug delivery systems further opens new avenues in PCOS management.

This comprehensive review provides an in-depth analysis of PCOS etiology, clinical implications, current treatment modalities, and future therapeutic innovations, aiming to bridge the gap between molecular understanding and effective clinical outcomes.

2. Keywords:

1. Polycystic Ovary Syndrome (PCOS)
2. Hyperandrogenism
3. Insulin Resistance
4. Metabolic Syndrome
5. Infertility
6. Hormonal Imbalance
7. Lifestyle Modification
8. Pharmacological Therapy
9. Metformin
10. Clomiphene Citrate
11. Ovulation Induction
12. Reproductive Endocrinology
13. Anti-Müllerian Hormone (AMH)
14. Novel Therapeutics
15. Endocrine Disorders

3: Introduction

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age, with a global prevalence ranging from 6% to 20% depending on diagnostic criteria and population diversity [1]. It

represents a heterogeneous and multifactorial condition characterized by hormonal imbalance, chronic anovulation, and polycystic ovarian morphology [2]. Clinically, PCOS manifests through menstrual irregularities, hyperandrogenism, infertility, obesity, and metabolic complications such as insulin resistance and dyslipidemia [3]. The syndrome is also recognized as a significant risk factor for the development of type 2 diabetes mellitus, cardiovascular disorders, and psychological disturbances [4].

The etiology of PCOS remains complex and incompletely understood. Current evidence suggests an interplay between genetic predisposition, neuroendocrine dysfunction, and environmental factors such as diet, stress, and lifestyle [5]. Insulin resistance, hyperinsulinemia, and elevated luteinizing hormone (LH) levels stimulate excessive androgen production from ovarian theca cells, disrupting normal follicular maturation [6]. This pathophysiological process leads to anovulation, follicular arrest, and the development of cystic ovarian structures [7].

Over the past two decades, advances in endocrinology and molecular biology have expanded the understanding of PCOS pathogenesis. The identification of key signaling pathways—such as the insulin receptor substrate (IRS), phosphoinositide 3-kinase (PI3K), and mitogen-activated protein kinase (MAPK) cascades—has linked metabolic dysfunction with reproductive abnormalities [8]. Moreover, inflammation, oxidative stress, and alterations in gut microbiota have emerged as critical contributors to disease progression [9].

Despite extensive research, PCOS remains underdiagnosed and often mismanaged due to its diverse presentation and overlapping symptoms with other metabolic and reproductive disorders [10]. Early diagnosis and individualized treatment are essential to minimize complications and improve reproductive outcomes.

This review aims to provide a comprehensive analysis of PCOS etiology, symptomatology, diagnosis, therapeutic approaches, and ongoing research innovations. It integrates current scientific knowledge with emerging pharmacological and technological advancements, offering insight into future directions for personalized management and therapeutic discovery in PCOS [11].

4: Pathophysiology of Polycystic Ovary Syndrome

The pathophysiology of Polycystic Ovary Syndrome (PCOS) is multifaceted, involving a complex interplay between genetic, hormonal, and metabolic factors [12]. It represents a state of endocrine dysregulation, characterized by hyperandrogenism, chronic anovulation, and insulin resistance [13]. These pathophysiological mechanisms collectively contribute to ovarian dysfunction and the diverse clinical manifestations observed in affected women.

4.1 Genetic and Epigenetic Factors

Genetic predisposition plays a central role in PCOS, as evidenced by familial clustering and twin studies [14]. Multiple susceptibility loci have been identified on chromosomes 2p16.3, 9q33.3, and 12q21.2, involving genes such as FSHR, LHCGR, INSR, and DENND1A [15]. These genes regulate gonadotropin signaling, insulin receptor function, and ovarian steroidogenesis. Additionally, epigenetic modifications—such as DNA methylation and histone acetylation—affect gene expression in ovarian and adipose tissues, influencing hormonal secretion and metabolic activity [16].

4.2 Neuroendocrine Dysfunction

The neuroendocrine axis, particularly the hypothalamic–pituitary–ovarian (HPO) system, exhibits dysregulation in PCOS [17]. Increased frequency of gonadotropin-releasing hormone (GnRH) pulses from the hypothalamus leads to elevated luteinizing hormone (LH) secretion, with relatively low or normal follicle-stimulating hormone (FSH) levels [18]. The elevated LH/FSH ratio promotes excessive androgen synthesis by ovarian theca cells, suppressing normal follicular development and ovulation [19]. This hormonal imbalance is a hallmark of PCOS pathophysiology.

4.3 Insulin Resistance and Hyperinsulinemia

Insulin resistance (IR) is a key metabolic feature of PCOS, affecting up to 70% of patients irrespective of body weight [20]. Hyperinsulinemia enhances ovarian androgen production by stimulating cytochrome P450c17α (CYP17A1) activity and reduces hepatic synthesis of sex hormone-binding globulin (SHBG), increasing free androgen levels [21]. Furthermore, impaired insulin signaling in skeletal muscle and adipose tissue leads to decreased glucose uptake and

lipid accumulation [22]. This metabolic disturbance creates a vicious cycle of obesity, inflammation, and hormonal dysregulation.

4.4 Role of Adipose Tissue and Obesity

Adipose tissue functions as an endocrine organ that secretes adipokines, cytokines, and inflammatory mediators [23]. In PCOS, adipose dysfunction contributes to insulin resistance and chronic low-grade inflammation. Elevated levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) have been reported in PCOS patients, linking obesity with metabolic and reproductive abnormalities [24]. Altered adipokine secretion—such as decreased adiponectin and increased leptin—further aggravates insulin resistance and androgen excess [25].

4.5 Ovarian Dysfunction and Follicular Arrest

The ovaries in PCOS display a thickened capsule and multiple small follicles that fail to mature due to defective folliculogenesis [26]. Excessive LH and insulin stimulation enhance theca cell androgen production, while suppressed FSH impairs granulosa cell aromatase activity, preventing estrogen conversion [27]. This hormonal imbalance leads to the arrest of antral follicle growth, resulting in anovulation and infertility [28]. The accumulation of immature follicles contributes to the characteristic "polycystic" ovarian morphology observed in ultrasound imaging.

4.6 Inflammation and Oxidative Stress

Chronic inflammation and oxidative stress are emerging contributors to PCOS pathogenesis [29]. Elevated reactive oxygen species (ROS) levels interfere with oocyte maturation, follicular development, and endometrial receptivity [30]. The activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway promotes pro-inflammatory cytokine production, exacerbating insulin resistance and androgen biosynthesis [31].

4.7 Gut Microbiota and Metabolic Dysbiosis

Recent studies have highlighted alterations in gut microbiota composition among women with PCOS [32]. Dysbiosis affects intestinal permeability, short-chain fatty acid (SCFA) production, and systemic inflammation. These changes influence glucose metabolism and androgen levels, suggesting that gut microbiota modulation may serve as a novel therapeutic target in PCOS management [33].

Summary of Pathophysiological Mechanisms

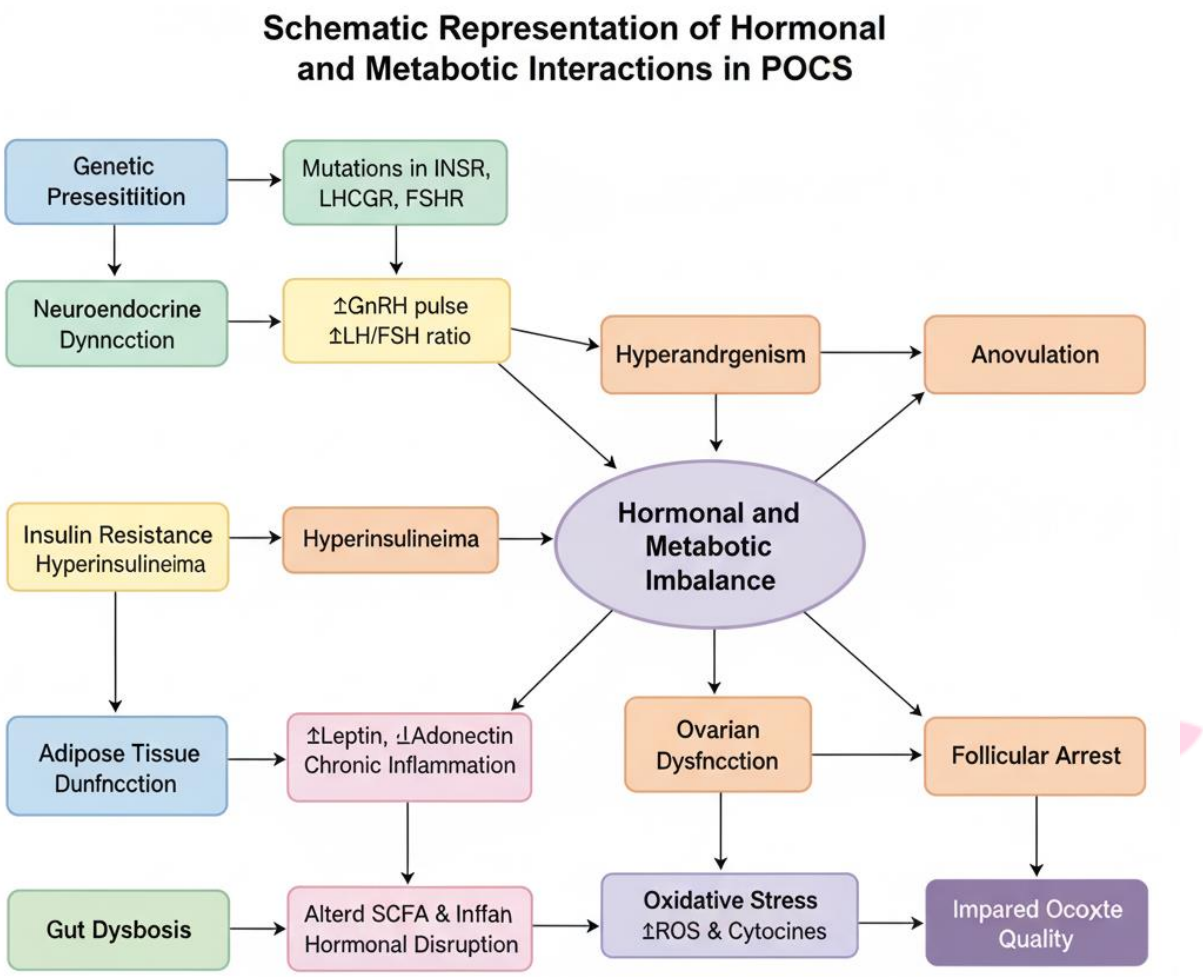


Figure 1: Schematic representation of hormonal and metabolic interactions contributing to PCOS pathophysiology.

The pathophysiology of PCOS is therefore not confined to a single pathway but reflects a multisystem disorder involving endocrine, metabolic, and inflammatory networks [34]. Understanding these interconnections is essential for developing targeted therapies aimed at restoring hormonal homeostasis, improving insulin sensitivity, and promoting ovarian function [35].

5: Symptoms of Polycystic Ovary Syndrome

Polycystic Ovary Syndrome (PCOS) exhibits a wide spectrum of clinical manifestations due to the complex interaction between endocrine, metabolic, and genetic factors [36]. The heterogeneity of symptoms makes diagnosis challenging and contributes to the syndrome's under-recognition among reproductive-aged women. Although not all individuals experience identical presentations, the hallmark features include menstrual irregularities, hyperandrogenic symptoms, infertility, and metabolic disturbances [37].

5.1 Menstrual Irregularities

Menstrual dysfunction is one of the earliest and most consistent manifestations of PCOS. It results from chronic anovulation caused by disrupted follicular maturation and hormonal imbalance [38]. Patients commonly present with oligomenorrhea (infrequent menstruation), amenorrhea (absence of menstruation), or dysfunctional uterine bleeding

[39]. These irregularities stem from persistent elevated luteinizing hormone (LH) levels and low or normal follicle-stimulating hormone (FSH) concentrations, which prevent the development of a dominant follicle [40]. The chronic anovulatory state also predisposes patients to endometrial hyperplasia due to prolonged unopposed estrogen exposure [41].

5.2 Hyperandrogenism and Its Clinical Manifestations

Hyperandrogenism, both biochemical and clinical, is a central feature of PCOS [42]. Elevated androgen levels—mainly testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS)—result in several external manifestations, including:

- Hirsutism: Excessive, male-pattern hair growth on the face, chest, and abdomen, affecting 60–70% of women with PCOS [43].
- Acne and Seborrhea: Increased sebum production leads to acne, particularly in the lower face and jawline region [44].
- Androgenic Alopecia: Thinning of scalp hair due to the miniaturization of hair follicles induced by elevated androgens [45].

These dermatological signs are often distressing for patients and significantly impact self-esteem and quality of life [46].

5.3 Infertility and Reproductive Dysfunction

Infertility is one of the most concerning outcomes of PCOS and is primarily due to chronic anovulation [47]. The failure of follicular maturation and irregular ovulation lead to reduced conception rates and increased early pregnancy loss [48]. Additionally, PCOS is associated with reduced oocyte quality and endometrial dysfunction, which impair implantation [49]. Altered secretion of hormones such as LH, FSH, progesterone, and insulin disrupts the hypothalamic-pituitary-ovarian (HPO) axis, further aggravating reproductive dysfunction [50].

5.4 Obesity and Metabolic Symptoms

Approximately 50–70% of women with PCOS are overweight or obese, with a predominance of central (visceral) obesity [51]. The accumulation of visceral fat contributes to insulin resistance, hyperinsulinemia, and dyslipidemia [52]. Metabolic symptoms commonly observed include impaired glucose tolerance, type 2 diabetes mellitus, hypertension, and elevated triglycerides [53]. The coexistence of these metabolic abnormalities increases the risk of cardiovascular disease and metabolic syndrome [54]. Even lean women with PCOS often exhibit some degree of insulin resistance and altered lipid metabolism [55].

5.5 Psychological and Emotional Disturbances

Psychological symptoms are frequently underdiagnosed in PCOS but are highly prevalent [56]. Women with PCOS are more likely to experience depression, anxiety, mood disorders, and body image dissatisfaction compared to the general population [57]. The cosmetic effects of hyperandrogenism, menstrual irregularities, and infertility collectively affect mental well-being [58]. Additionally, chronic inflammation, dysregulated cortisol levels, and sleep disturbances may exacerbate psychiatric symptoms [59].

5.6 Long-Term Complications

If untreated, PCOS can lead to several long-term complications, including type 2 diabetes mellitus, endometrial carcinoma, non-alcoholic fatty liver disease (NAFLD), and cardiovascular disease [60]. Persistent anovulation increases the risk of endometrial hyperplasia, while chronic metabolic disturbances predispose individuals to atherosclerosis and insulin-related disorders [61]. These comorbidities highlight the systemic nature of PCOS and the necessity for early diagnosis and sustained management [62].

5.7 Summary of Symptoms and Complications

Summary Symptoms and Complications in PCOS

Category	Symptoms / Complications	Underdying Mechanism
Reproductive	Oligomenerra, Amentorra, Infetrility	Anovulation due hormonal imblance
Hyperandargenic	Hirsitum, Acne, Aloopiha	Elevated andrgen secration
Metabolic	Obesity, Dyslipiemdia	Impaired glucose
	Insulin Resistance	Impaired glucose matabotium
Psychological	Anxiety, Depression, Mood swings	Hormonal and emational dysreguation
Long-term	Diabetes, Endememial carcioma, NAFLD, CVD	
	Chronic metabollic and endortine dysfnsction	

Figure 2: Clinical spectrum of Polycystic Ovary Syndrome, illustrating interlinked reproductive, metabolic, and psychological manifestations.

PCOS symptoms vary widely in severity and presentation, with each phenotype reflecting a distinct combination of endocrine and metabolic disturbances [63]. Recognizing these symptoms early is crucial for prompt intervention, reducing disease progression, and preventing associated comorbidities [64]. A comprehensive clinical evaluation is therefore essential for accurate diagnosis and individualized management of PCOS [65].

6: Diagnosis of Polycystic Ovary Syndrome

Accurate diagnosis of Polycystic Ovary Syndrome (PCOS) is essential for timely intervention, prevention of long-term complications, and individualized treatment planning [66]. Due to the heterogeneity of clinical manifestations, diagnosis often requires a combination of clinical evaluation, biochemical assays, and imaging studies [67]. Multiple criteria have been established to standardize diagnosis, with the Rotterdam, NIH, and AE-PCOS criteria being the most widely accepted [68].

6.1 Diagnostic Criteria

6.1.1 Rotterdam Criteria (2003)

The Rotterdam criteria require the presence of two out of three features for a PCOS diagnosis [69]:

1. Oligo- or anovulation
2. Clinical and/or biochemical hyperandrogenism
3. Polycystic ovarian morphology (≥12 follicles per ovary or increased ovarian volume >10 cm^3) on ultrasound

These criteria are widely used in clinical practice and research due to their inclusivity and flexibility [70].

6.1.2 NIH Criteria (1990)

The NIH criteria emphasize hyperandrogenism and chronic anovulation as mandatory for diagnosis, excluding polycystic ovarian morphology [71]. This stricter definition helps identify women with a more severe metabolic and reproductive phenotype [72].

6.1.3 AE-PCOS Society Criteria (2006)

The Androgen Excess and PCOS Society (AE-PCOS) criteria require hyperandrogenism plus ovarian dysfunction, either oligo-anovulation or polycystic ovaries [73]. These criteria focus on the pathogenic role of androgen excess and are useful for identifying patients at higher risk for metabolic complications [74].

6.2 Clinical Evaluation

A comprehensive history and physical examination are the first steps in PCOS diagnosis [75]. Key assessments include
Menstrual history: Duration, regularity, and frequency
Signs of hyperandrogenism: Hirsutism (Ferriman–Gallwey score), acne, androgenic alopecia
Anthropometric measurements: Body mass index (BMI), waist-to-hip ratio
Blood pressure assessment: To evaluate cardiovascular risk factors [76]

6.3 Biochemical Assessment

Laboratory investigations are crucial for confirming hyperandrogenism, evaluating ovulatory status, and assessing metabolic risk [77]. Common tests include:
Hormonal assays: Total and free testosterone, DHEAS, androstenedione, LH, FSH, estradiol, and prolactin
Insulin and glucose metabolism: Fasting insulin, fasting glucose, oral glucose tolerance test (OGTT)
Lipid profile: Total cholesterol, LDL, HDL, triglycerides
Anti-Müllerian Hormone (AMH): Elevated AMH levels correlate with increased ovarian follicle count and can support diagnosis [78]

6.4 Imaging Studies

Transvaginal ultrasonography (TVUS) is the imaging modality of choice for assessing ovarian morphology [79]. Diagnostic features include:

- ≥12 small follicles (2–9 mm) in each ovary
- Increased ovarian volume (>10 cm^3)
- "String-of-pearls" appearance due to peripheral follicle arrangement [80]

Advanced imaging, such as magnetic resonance imaging (MRI), may be used in atypical cases or research settings [81].

6.5 Exclusion of Other Disorders

PCOS is a diagnosis of exclusion, as several conditions mimic its clinical features [82]:

- Congenital adrenal hyperplasi
- Cushing's syndrome
- Androgen-secreting tumors
- Thyroid dysfunction
- Hyperprolactinemia

Laboratory evaluation and imaging are used to rule out these differential diagnoses [83].

6.6 Phenotypes of PCOS

Based on the Rotterdam criteria, four major phenotypes have been identified [84]:

1. Phenotype A: Hyperandrogenism + ovulatory dysfunction + polycystic ovaries
2. Phenotype B: Hyperandrogenism + ovulatory dysfunction
3. Phenotype C: Hyperandrogenism + polycystic ovaries
4. Phenotype D: Ovulatory dysfunction + polycystic ovaries

Phenotype classification helps guide personalized therapy and predicts metabolic and reproductive risks [85].

6.7 Summary of Diagnostic Approach

Diagnostic Components of Polycsstic Ovary Syndrome (PCOS)

Diagnostic Component	Evaluation Method	Clinical Significance
Clinical Signs	Hirsutum, acne, alopaia	Detect hyperandrgenism
Biochemical Tests	Tesstetrone, DHEAS, LH/FSH ratio, AMH	Confrim hormonal imbalance
Metaboltic Tests	OGTT, insulin, imbalance	Assess metabolic risk
Imaging	OGTT, insulin, lipid profile	Assess metabolic risk
Exclusion	Transvaginal ulrstound	Identify polycystic ovarian morthology
Exclusion admor, screeing	Thyroid, adrenal, tumor tumor screeing	Rule out other disorders

Figure 3: Diagnostic workflow for PCOS integrating clinical, biochemical, and imaging parameters.

The diagnosis of PCOS requires a multifaceted approach, combining clinical observation, laboratory evaluation, and imaging while excluding other endocrine disorders. Accurate diagnosis is critical for tailored management, reducing the risk of long-term reproductive, metabolic, and psychological complications [86].

7: Management / Treatment of Polycystic Ovary Syndrome

Effective management of Polycystic Ovary Syndrome (PCOS) requires a multidisciplinary approach tailored to the patient's clinical phenotype, reproductive goals, and metabolic profile [87]. Treatment strategies aim to restore menstrual regularity, improve ovulation, reduce hyperandrogenic symptoms, and address metabolic complications [88]. Management can be broadly categorized into lifestyle modification, pharmacological therapy, and surgical interventions.

7.1 Lifestyle Modification

Lifestyle intervention is the first-line therapy for all PCOS patients, regardless of BMI [89]. Key components include:

Dietary Modification: A hypocaloric, low-glycemic index (GI) diet helps reduce insulin resistance, body weight, and androgen levels [90]. Nutrient-rich diets emphasizing whole grains, lean proteins, fruits, and vegetables are recommended.

Physical Activity: Regular exercise (≥150 min/week) improves insulin sensitivity, promotes weight loss, and reduces cardiovascular risk [91]. Both aerobic and resistance training are beneficial.

Behavioral Therapy: Psychological support and stress management techniques, such as cognitive-behavioral therapy (CBT) or mindfulness, improve adherence to lifestyle changes and reduce anxiety or depression associated with PCOS [92].

Even a 5–10% weight loss in overweight patients can restore ovulation and improve metabolic parameters [93].

7.2 Pharmacological Therapy

Pharmacotherapy is indicated when lifestyle modification alone is insufficient or when specific symptoms require targeted intervention [94].

7.2.1 Insulin Sensitizers

Metformin is the most widely used insulin sensitizer. It improves insulin sensitivity, reduces hyperinsulinemia, and indirectly lowers androgen production [95]. Metformin also aids in restoring menstrual cyclicity and ovulation, especially in women with metabolic syndrome or glucose intolerance [96].

7.2.2 Ovulation Induction Agents

Clomiphene Citrate (CC): Selective estrogen receptor modulator that induces ovulation by increasing FSH levels. Standard first-line therapy for anovulatory infertility [97].

Letrozole: Aromatase inhibitor that lowers estrogen feedback, enhancing FSH secretion and ovulation. Recent studies show higher live birth rates compared to CC [98].

7.2.3 Oral Contraceptives

Combined oral contraceptives (COCs) regulate menstrual cycles, reduce androgen levels, and alleviate hirsutism and acne [99]. They also provide endometrial protection against hyperplasia.

7.2.4 Anti-Androgens

Spironolactone, cyproterone acetate, or flutamide can be used to treat hirsutism, acne, and androgenic alopecia [100] Anti-androgens are often combined with COCs to improve efficacy and reduce teratogenic risk [101].

7.3 Surgical Intervention

Surgery is considered second-line therapy for patients resistant to pharmacological treatments [102]:
Laparoscopic Ovarian Drilling (LOD): Surgical destruction of a portion of ovarian tissue to reduce androgen production and restore ovulation. LOD can improve fertility in women unresponsive to ovulation induction agents [103].
Bariatric Surgery: Considered in morbidly obese patients with PCOS to improve metabolic outcomes and fertility [104].

7.4 Holistic and Integrative Approaches

Complementary approaches may enhance standard therapy outcomes [105]:
Yoga and Mindfulness: Reduce stress, improve insulin sensitivity, and support reproductive health.
Nutraceuticals: Inositol isomers (myo-inositol and D-chiro-inositol) improve insulin resistance, ovulation, and hormonal balance [106].
Herbal Supplements: Limited but promising evidence exists for cinnamon, spearmint, and green tea in managing metabolic and androgenic symptoms [107].

7.5 Individualized Management

Management strategies should be personalized based on:

- Patient age and reproductive goals
- Phenotype (hyperandrogenic, metabolic, or reproductive)
- Presence of obesity or metabolic syndrome
- Psychological and quality-of-life considerations [108]

An integrated multidisciplinary approach, including endocrinologists, gynecologists, dietitians, and mental health professionals, ensures optimal outcomes [109].

Summary of PCOS Management Approaches

Liferapy Type	Examples	Clinical Benefit
Diet, Exercise Behavioral therapy	Weight reduction, insulin sensitivity, menstual regulation	Weight reduction, improved insulin sensitivity, menstrual regulation
Pharmaological	Metfforin, Letrozole, Climphip, COCS, Anti-andargens	Ovulation induction, hirsistimt reduction, androgen suppresion
Integrative Yoga, Insozitl, Herbal supplements	Laprapoossic Ovarin Drilling, Barratic Surgery	Fertility improvement, benefits Stress reduction, regulation, hormonal balance

Figure 4: Algorithm for PCOS management integrating lifestyle, pharmacological, and surgical interventions.

Effective treatment of PCOS requires a combination of interventions tailored to the patient's phenotype and goals. While lifestyle modification remains foundational, pharmacological and surgical therapies provide targeted improvements in metabolic, reproductive, and androgenic outcomes [110].

8: Drugs Required for Treatment of PCOS

Pharmacological intervention plays a pivotal role in the management of Polycystic Ovary Syndrome (PCOS), particularly in restoring ovulation, regulating menstrual cycles, reducing hyperandrogenism, and improving metabolic parameters. Among various agents, Metformin and Letrozole are widely used and have robust evidence supporting their efficacy in different PCOS phenotypes [111]

8.1 Metformin

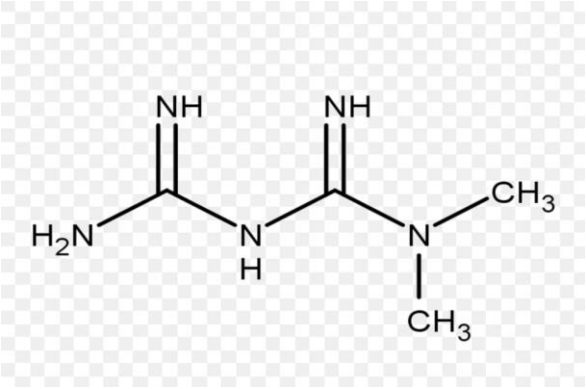
8.1.1 Introduction and Classification

Metformin is a biguanide class oral antihyperglycemic agent primarily used for type 2 diabetes mellitus [112]. In PCOS, Metformin is employed for its insulin-sensitizing properties, improving glucose homeostasis and reducing hyperinsulinemia, which indirectly decreases ovarian androgen production [113].

8.1.2 Chemical Structure

IUPAC Name: *N,N-dimethylimidodicarbonimidic diamide*
Molecular Formula: *C4H11N5O*

Structure:



8.1.3 Mechanism of Action

Metformin exerts its therapeutic effects via multiple mechanisms [114]:

- Hepatic Effects: Reduces gluconeogenesis, lowering fasting plasma glucose.
- Peripheral Effects: Enhances insulin-mediated glucose uptake in skeletal muscle and adipose tissue.
- Ovarian Effects: Decreases ovarian androgen production and improves ovulatory function.
- Metabolic Effects: Reduces insulin resistance, body weight, and cardiovascular risk markers.

8.1.4 Pharmacokinetics

Absorption: Oral bioavailability ~50–60%

Distribution: Widely distributed; minimal plasma protein binding

Metabolism: Not metabolized; excreted unchanged via kidneys

Half-life: 4–6 hours

Excretion: Renal (unchanged) [115]

8.1.5 Clinical Applications in PCOS

1. Restoration of regular menstrual cycles
2. Induction of ovulation in women with anovulatory infertility
3. Improvement of insulin resistance and glucose tolerance
4. Reduction of androgen levels and associated symptoms (hirsutism, acne) [116]

8.1.6 Adverse Effects

Gastrointestinal discomfort (nausea, diarrhea, abdominal pain)

Rare risk of lactic acidosis in renal impairment

Vitamin B12 deficiency with long-term use [117]

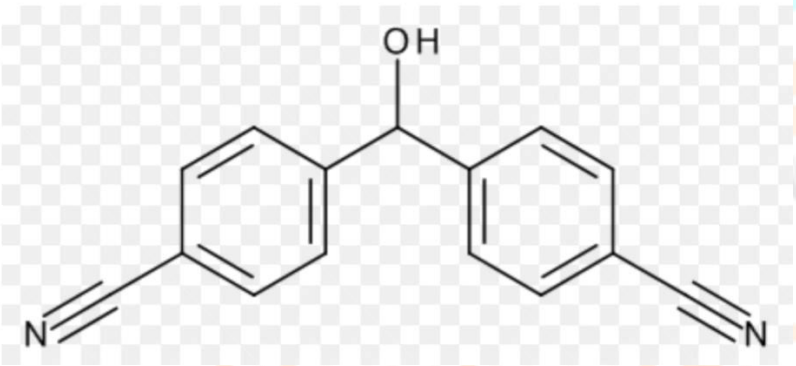
8.2 Letrozole

8.2.1 Introduction and Classification

Letrozole is a non-steroidal aromatase inhibitor that prevents the conversion of androgens to estrogens [118]. In PCOS, it is used for ovulation induction, particularly in women who are resistant to Clomiphene Citrate [119].

8.2.2 Chemical Structure

IUPAC Name: 4,4'-(1H-1,2,4-Triazol-1-ylmethylene)dibenzonitrile
Molecular Formula: C17H11N5
Structure:



8.2.3 Mechanism of Action

Letrozole works by [120]:

- Inhibiting aromatase enzyme, reducing estrogen synthesis
- Lowering circulating estrogen levels, which releases negative feedback on the hypothalamic-pituitary axis
- Increasing FSH secretion, promoting follicular growth and ovulation
- Does not have anti-estrogenic effects on the endometrium or cervical mucus, improving fertility outcomes compared to Clomiphene Citrate [121]

8.2.4 Pharmacokinetics

- Absorption: Rapid oral absorption; peak plasma concentration ~1 hour
- Distribution: High plasma protein binding (~60%)

- Metabolism: Hepatic via CYP3A4 and CYP2A6
- Half-life: ~2 days
- Excretion: Urine and feces [122]

8.2.5 Clinical Applications in PCOS

Induction of ovulation in anovulatory women

Improvement in ovulation and live birth rates compared to Clomiphene Citrate

Used in combination with lifestyle modification for optimal outcomes [123]

8.2.6 Adverse Effects

Mild fatigue, dizziness, and headache

Rare risk of ovarian cyst formation or multiple gestations

Minimal impact on endometrial thickness, generally well tolerated [124]

Comparison of Metmorin and Letrozole in POS Treatment

Drug		Primary Use in POCS	Adverse Effect Effects
Metmfforin	Insulin sensttizer; reduces hepatic glucose production	Improve insulin resistance; induce ovolation; regulate regulate menses	GI upset, B12 deficiency, rare lactic aciosis
Biguanide	Inhibits estrgen synstesis → ovulation	Inhibits estrrgen synshesis → ↑FSH ↑FSH → ovolation	Headache, dizznesis
Letrozole	Aromatase inhibitor	Ovulation induction in anovalory women	rare dizisnis, multiple pregnancy

Figure 5: Structural diagrams of Metformin and Letrozole highlighting functional groups.

Both Metformin and Letrozole play complementary roles in PCOS management. Metformin addresses metabolic dysfunction, while Letrozole specifically targets reproductive dysfunction, providing an integrated approach to restoring hormonal balance and improving fertility outcomes [125].

9: Preventive and Supporting Care in PCOS

Polycystic Ovary Syndrome (PCOS) is a chronic endocrine and metabolic disorder with lifelong implications for reproductive, metabolic, and psychological health. While pharmacological therapy addresses immediate symptoms, preventive measures and supportive care are critical for reducing disease progression, minimizing complications, and improving overall quality of life [126].

9.1 Lifestyle and Dietary Interventions

Lifestyle modification is the cornerstone of both prevention and management in PCOS [127]:

Weight Management: Achieving and maintaining a healthy BMI (18.5–24.9 kg/m²) reduces insulin resistance, lowers androgen levels, and restores ovulatory function [128].

Balanced Diet: Emphasis on low-glycemic index carbohydrates, lean proteins, and healthy fats can improve metabolic outcomes [129]. Diet rich in fiber, vitamins, and minerals supports hormonal balance and reduces inflammation.

Physical Activity: Regular aerobic and resistance exercise enhances insulin sensitivity, reduces central adiposity, and improves cardiovascular health [130].

Even a 5–10% reduction in body weight can significantly improve menstrual regularity and fertility outcomes [131].

9.2 Early Screening and Risk Assessment

Preventive care involves early detection of metabolic, cardiovascular, and reproductive risks [132]:

- Glucose Tolerance and Insulin Assessment: Early identification of impaired glucose tolerance or insulin resistance allows timely intervention [133].
- Lipid Profile Monitoring: Routine evaluation for dyslipidemia prevents long-term cardiovascular complications [134].
- Blood Pressure Assessment: Detects hypertension and cardiovascular risk early [135].
- Endometrial Health: Monitoring for hyperplasia or irregular bleeding reduces the risk of endometrial carcinoma [136].
- Early screening is particularly crucial in adolescents and women planning pregnancy.

9.3 Psychological Support

Psychological well-being is a major component of supportive care [137]:

- Counseling and Therapy: Cognitive-behavioral therapy (CBT) and supportive counseling help manage anxiety, depression, and body image concerns associated with hyperandrogenism and infertility [138].
- Stress Management: Mindfulness, yoga, and meditation reduce cortisol levels and improve insulin sensitivity [139].

Addressing psychological symptoms enhances treatment adherence and overall quality of life.

9.4 Nutritional Supplements and Complementary Care

Certain nutraceuticals and supplements support metabolic and reproductive health in PCOS [140]:

- Inositols (Myo-Inositol and D-Chiro-Inositol): Improve insulin sensitivity, restore ovulation, and normalize menstrual cycles [141].
- Vitamin D: Deficiency is common in PCOS and supplementation improves insulin resistance and ovulatory function [142].
- Omega-3 Fatty Acids: Anti-inflammatory effects support metabolic health and reduce androgen levels [143].
- Probiotics: Modulation of gut microbiota may improve insulin sensitivity and reduce systemic inflammation [144].

9.5 Patient Education and Awareness

Empowering patients with knowledge about PCOS is essential for long-term disease control [145]:

- Educate about the chronic nature of PCOS and its systemic effects
- Encourage adherence to lifestyle and pharmacological interventions
- Discuss reproductive planning and fertility options
- Raise awareness of potential long-term complications, such as diabetes, cardiovascular disease, and endometrial cancer [146]

9.6 Preventive Strategies in Adolescents

Early intervention in adolescence can prevent progression of metabolic and reproductive complications [147]:

- Promote healthy lifestyle habits from early puberty
- Monitor menstrual cycles and hyperandrogenic signs
- Early referral to endocrinologists or gynecologists for high-risk individuals [148]

Summary of Preventive and Supporting Care

Figure 6: Integrated preventive and supportive care model for PCOS.

Summary of Preventive and Supporting Care in PCOS

Preventive Aspect	Intervention	Expected Benefit
Lifestyle	Weight management, exercise, low-GI diet	Reduced insulin resistance, improved ovalation
Early Screening	Glucose, lipids, BP, enderemtial health	Early detection of metabolic and reproducive risks
Psycholoical Support	CBT, counseling stress management	Improved mental health and treatment adherance
Nutritional Supplements	Insotol, Vitamin D, Omega-3, probotics	Metabotic and reproductive support
Patient Education	Awareness programs, reproductive counseling outcomes	Better self-management and long ad-term outcomes

Preventive and supportive care in PCOS is multidimensional, addressing metabolic, reproductive, and psychological domains. Early intervention, combined with patient education and lifestyle modification, significantly reduces long-term complications and enhances quality of life for women with PCOS [149].

10: Recent Research / Advances in PCOS

Ongoing research in Polycystic Ovary Syndrome (PCOS) focuses on unraveling molecular mechanisms, improving therapeutic efficacy, and developing personalized treatment strategies. Advances in genomics, metabolomics, and nanotechnology have transformed understanding and management of this complex disorder [150].

10.1 Molecular and Genetic Insights

Recent studies have identified novel genetic loci and epigenetic modifications associated with PCOS susceptibility [151]:

- Variants in DENND1A, THADA, FSHR, and LHCGR genes contribute to hyperandrogenism and ovulatory dysfunction [152].

- Epigenetic changes, including DNA methylation and histone acetylation, influence ovarian and metabolic gene expression [153].
- Transcriptomic and proteomic analyses reveal altered signaling pathways in insulin resistance, inflammation, and steroidogenesis [154].
- These discoveries enable targeted interventions aimed at molecular drivers of PCOS.

10.2 Novel Pharmacological Approaches

Emerging pharmacotherapies focus on precision medicine and multitargeted mechanisms [155]:

- Inositol Isomers: Myo-inositol and D-chiro-inositol enhance insulin signaling, reduce hyperandrogenism, and restore ovulatory cycles [156].
- GLP-1 Receptor Agonists (e.g., Liraglutide): Improve weight loss, insulin sensitivity, and cardiovascular outcomes in obese PCOS patients [157].
- SGLT2 Inhibitors: Under investigation for metabolic improvement and reduction of androgen excess [158].
- Anti-inflammatory Agents: Targeting TNF-α, IL-6, and oxidative stress shows promise in mitigating metabolic and reproductive disturbances [159].

10.3 Nutraceutical and Herbal Interventions

Natural compounds and supplements are gaining attention for their safety and efficacy:

- Cinnamon Extract: Enhances insulin sensitivity and reduces fasting glucose [160].
- Spearmint Tea: Demonstrates anti-androgenic effects and reduces hirsutism [161].
- Vitamin D and Omega-3 Fatty Acids: Improve insulin resistance and inflammatory markers [162].

10.4 Role of Gut Microbiota and Probiotics

Emerging evidence links gut dysbiosis to PCOS pathophysiology:

- Altered microbiota composition influences insulin resistance, androgen levels, and inflammation [163].
- Probiotic supplementation and dietary fiber interventions restore microbial balance and improve metabolic parameters [164].

10.5 Nanomedicine and Drug Delivery Innovations

Nanotechnology is being explored to enhance drug bioavailability and targeted delivery:

Nanoformulations of Metformin and Inositols improve pharmacokinetics and tissue-specific delivery [165].

Liposomal and nanoparticle-based delivery systems are being tested for controlled release and reduced side effects [166].

10.6 Assisted Reproductive Technologies (ART) Advances

PCOS-related infertility benefits from recent ART innovations:

Individualized ovarian stimulation protocols reduce risk of ovarian hyperstimulation syndrome (OHSS) [167].

In vitro maturation (IVM) of oocytes offers safer fertility options for women with severe PCOS [168].

10.7 Personalized Medicine and Future Therapeutics

Integration of genomic, metabolomic, and phenotypic data enables individualized treatment planning [169].

Gene therapy and RNA-based interventions targeting androgen synthesis and insulin signaling pathways are under preclinical evaluation [170].

AI-driven predictive models assist in optimizing ovulation induction and metabolic management [171].

Summary of Preventive and Supporting Care in PCOS

Preventive Aspect	Intervention	Expected Benefit
Lifestyle	Weight management, exercise, low-GI diet	Reduced insulin resistance, improved ovalation
Early Screening	Glucose, lipids, BP, enderemtial health	Early detection of metabolic and reproducive risks
Psychololical Support	CBT, counseling stress management	Improved mental health and treatment adherance
Nutritional Supplements	Insotol, Vitamin D, Omega-3, probotics	Metabotic and reproductive support
Patient Education	Awareness programs, reproductive counseling outcomes	Better self-management and long ad-term outcomes

Figure 7: Emerging therapeutic targets and molecular pathways in PCOS.

Advances in molecular biology, pharmacology, and technology have shifted PCOS management toward precision medicine. Combining targeted drug therapy, nutraceuticals, lifestyle intervention, and assisted reproductive techniques has the potential to significantly improve clinical outcomes and reduce long-term comorbidities in women with PCOS [172].

11: Graphs and Images for PCOS

Visual aids enhance understanding of the complex pathophysiology, clinical manifestations, and therapeutic approaches in Polycystic Ovary Syndrome (PCOS) [173]. The following are suggested figures and charts for inclusion in the paper:

11.1 Figure 1 – Pathophysiology of PCOS

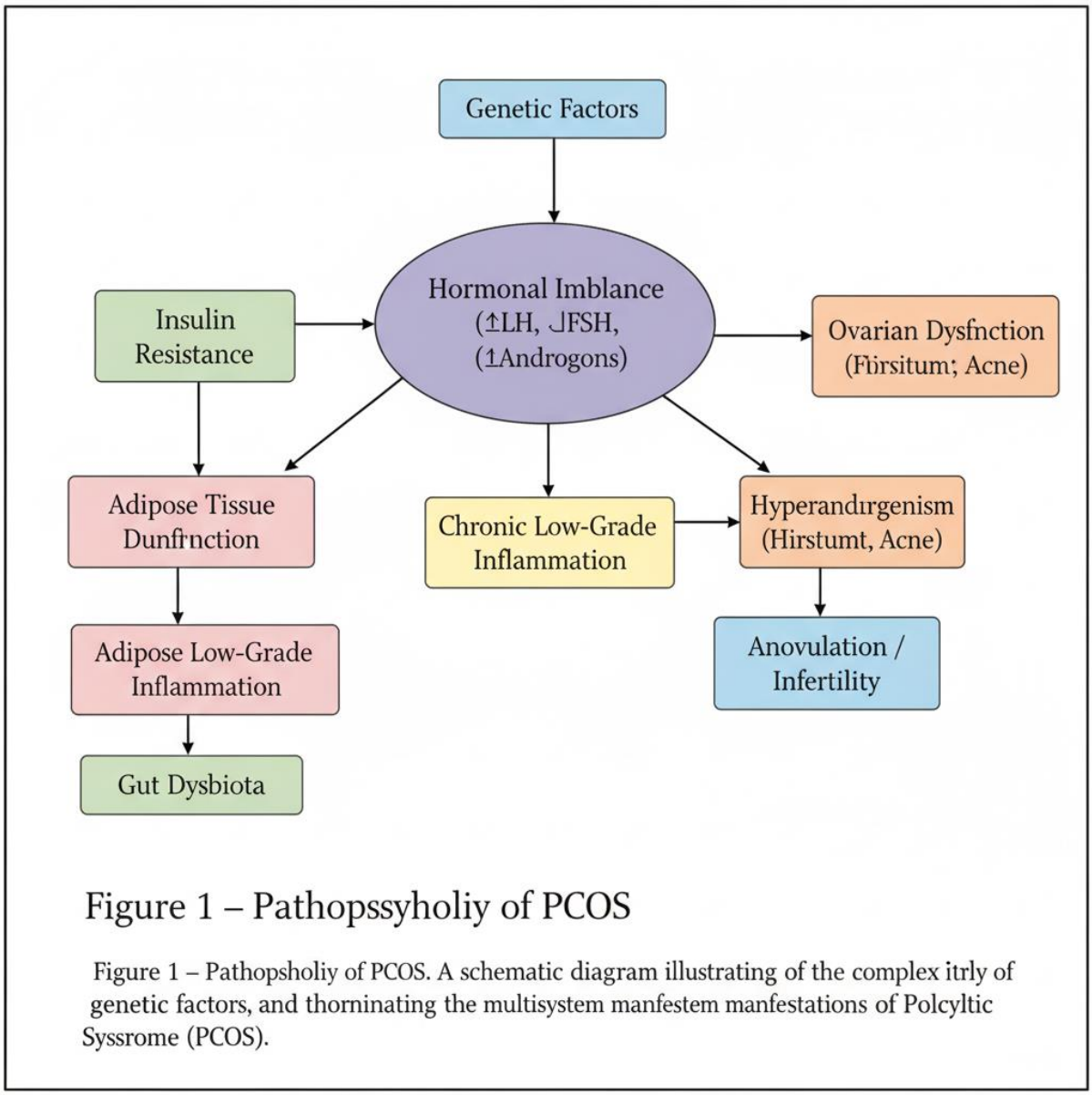


Figure 1 – Pathopssyholiy of PCOS

Figure 1 – Pathopsholiy of PCOS. A schematic diagram illustrating of the complex itrly of genetic factors, and thorninating the multisystem manfestem manfestations of Polcyltic Syssrome (PCOS).

11.2 Figure 2 – Clinical Spectrum of PCOS

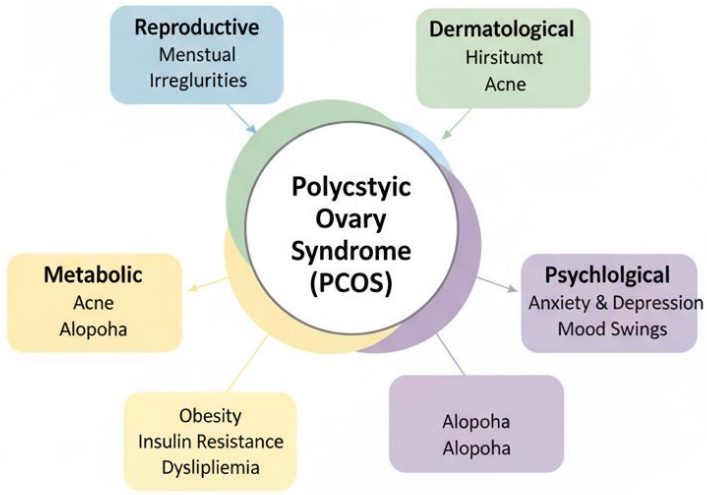


Figure 2 – Clinical Spectrum of PCOS. An illustration of the diverse reproductive, mantisitatons and manfiestations of Polycssic Ovary Syndrome.

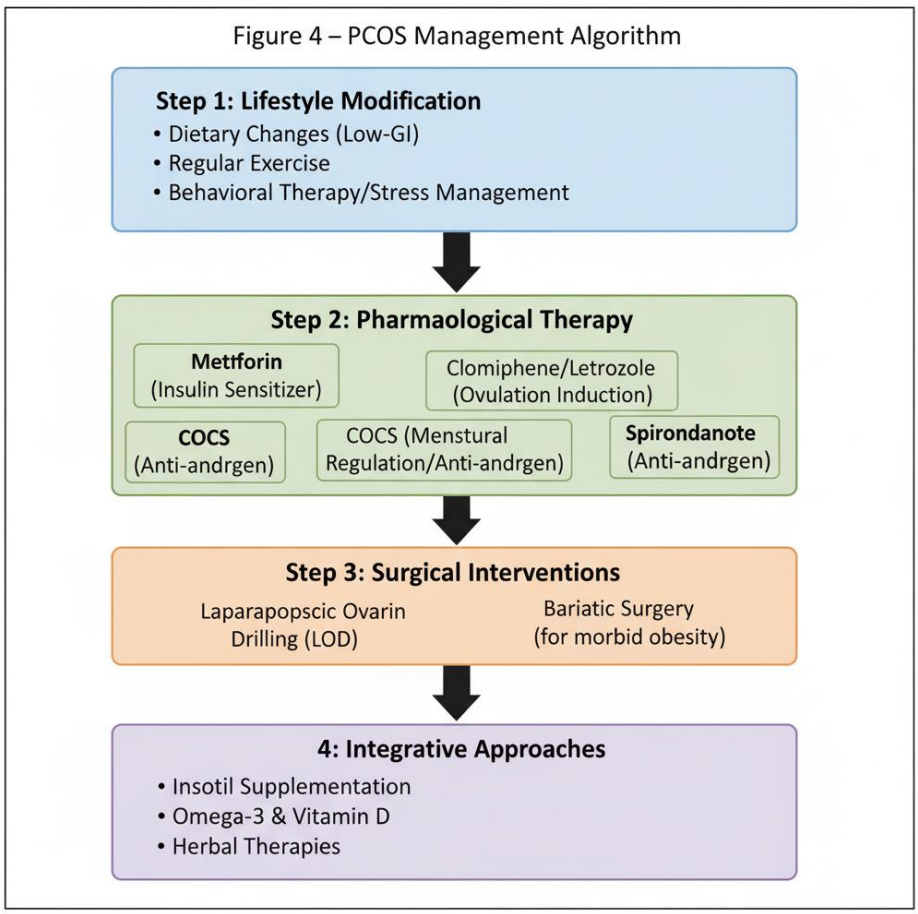
11.3 Figure 3 – Diagnostic Workflow

Description: Flowchart integrating:

1. Clinical assessment (menstrual history, hyperandrogenism)
2. Biochemical tests (hormonal and metabolic evaluation)
3. Imaging (transvaginal ultrasound)
4. Exclusion of other disorders

Purpose: Guides clinicians in systematic diagnosis.

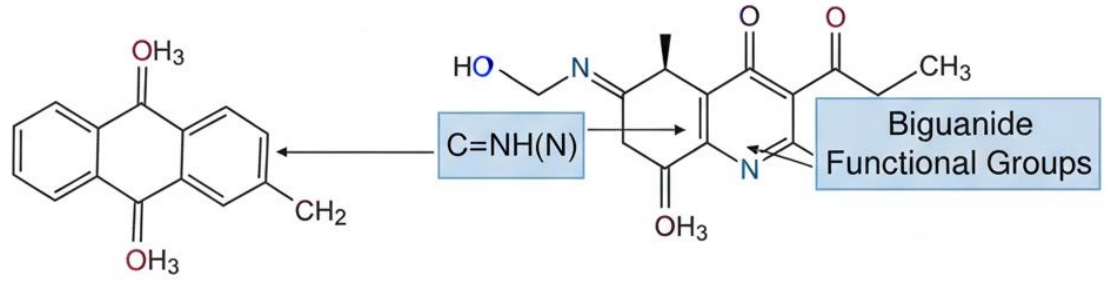
11.4 Figure 4 – Management Algorithm



11.5 Figure 5 – Chemical Structures of Key Drugs

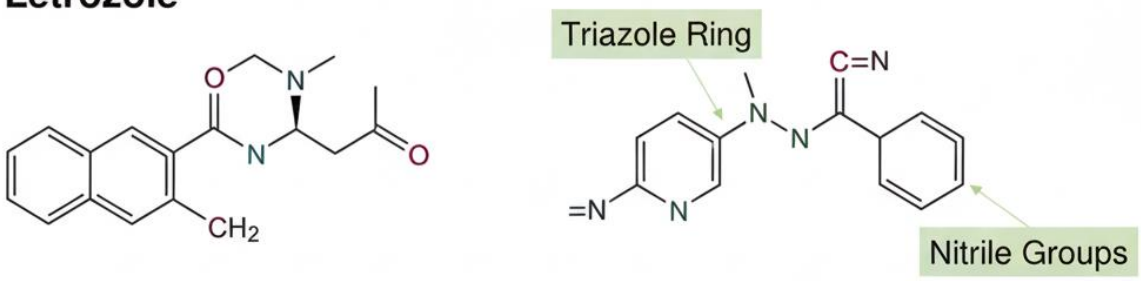
Figure 5 – Chemical Structures of Key Drugs in in POS Treatment

Metmorin



(A). Metforin Biguanide functional Groups

Letrozole



(A). Letuanide Functional on Letroole

Illustrats the molecular structures and key functional groups of Metfforin and Letrzole, providing a structural basis for their therapetic actions in PCS.

11.6 Figure 6 – Preventive and Supportive Care Model

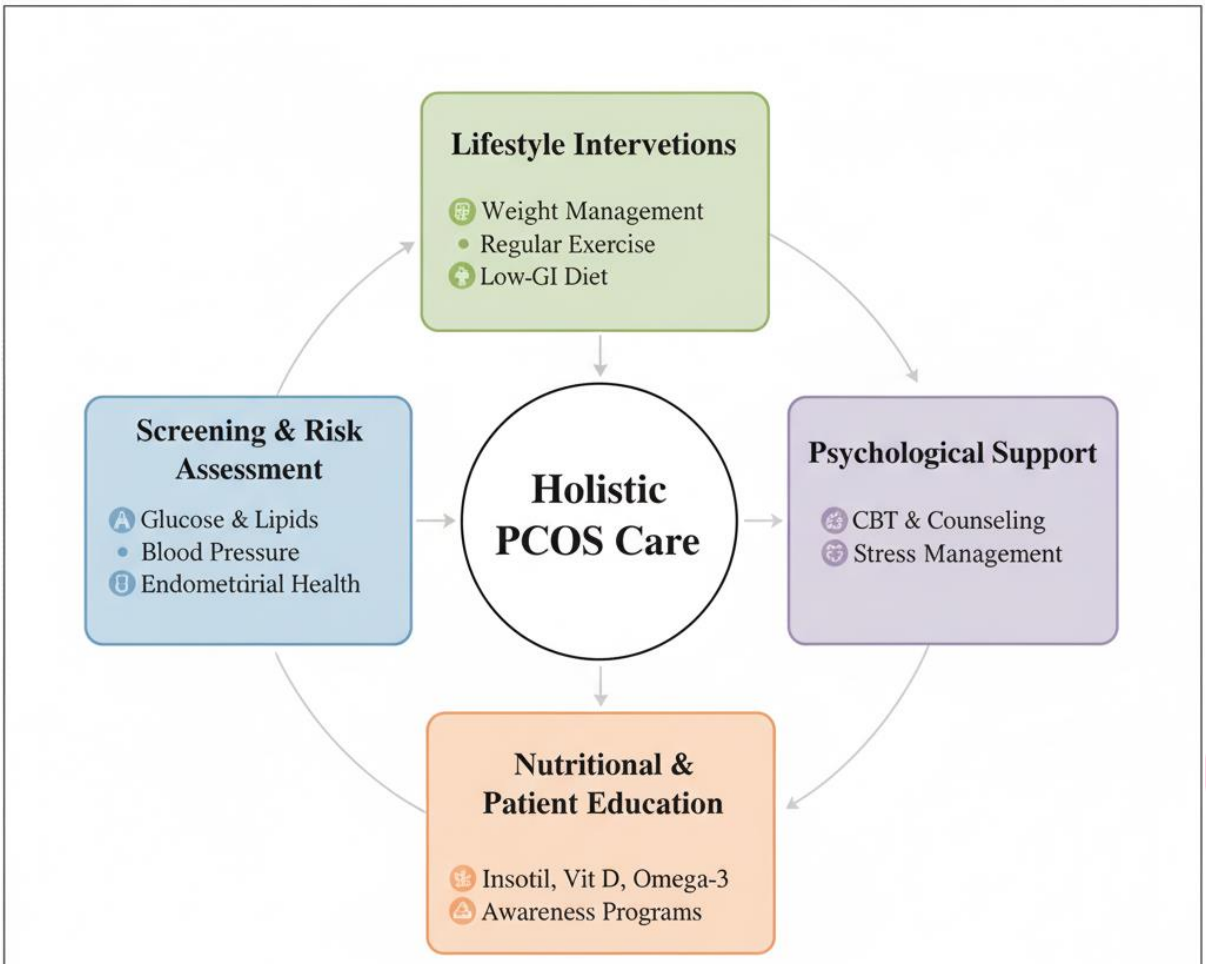


Figure 6 – Preventive and Supportive Care Model
A multi-level schematic illustrating a holistic, integrated care approach for management management and long-tem iog-term complications in Polcytlyc Ovaary Synsrome.

11.7 Figure 7 – Emerging Therapeutic Targets

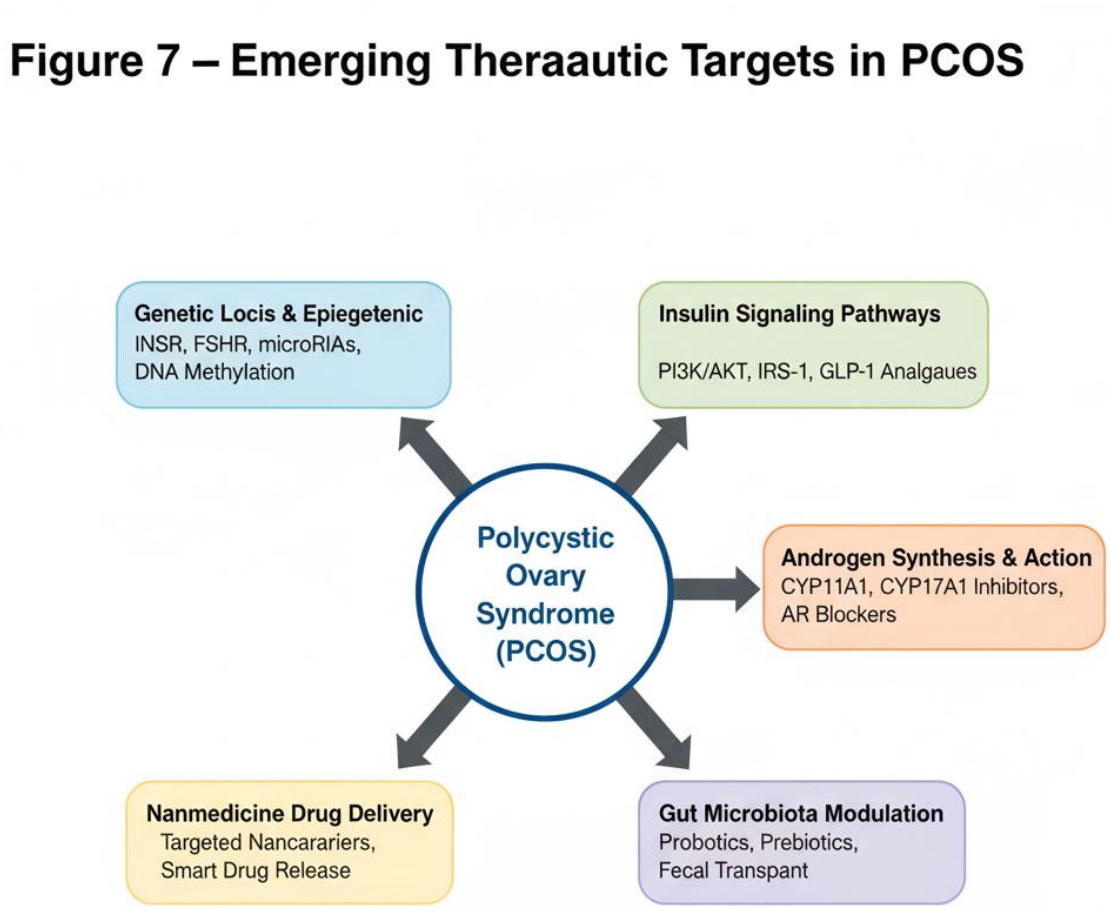


Figure 7 – Emerging Theraeutic in PCOS. A schemtic diagram future theraeutic directions by illustrating key molecular targets and pathways infolvays involved in the phathypology of Polcysstic Syndrome.

11.8 Graph 1 – Prevalence of PCOS Symptoms

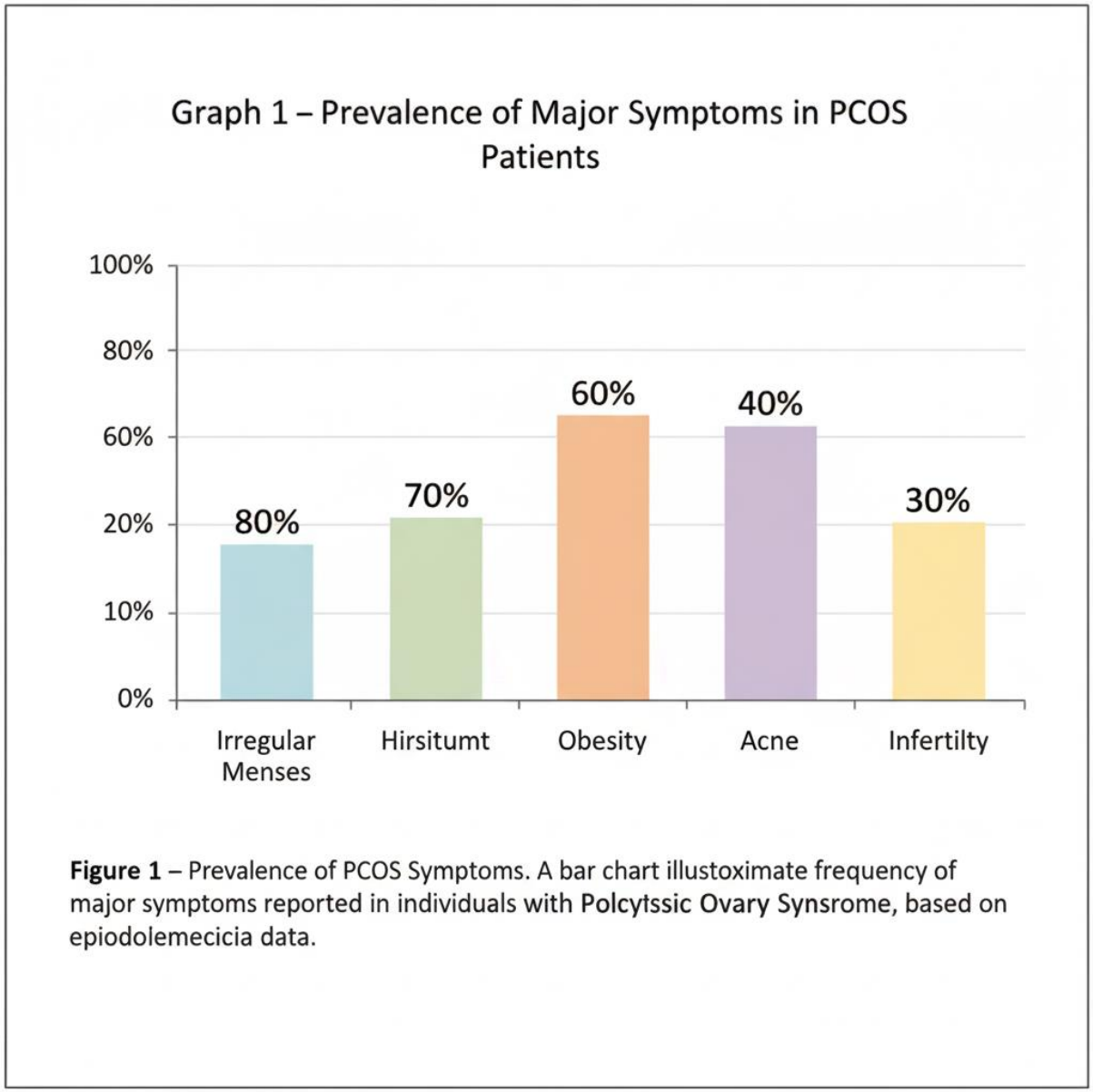


Figure 1 – Prevalence of PCOS Symptoms. A bar chart illustoximate frequency of major symptoms reported in individuals with **Polcytssic Ovary Synsrome**, based on epiodolemecicia data.

11.9 Graph 2 – Metabolic Parameters in PCOS

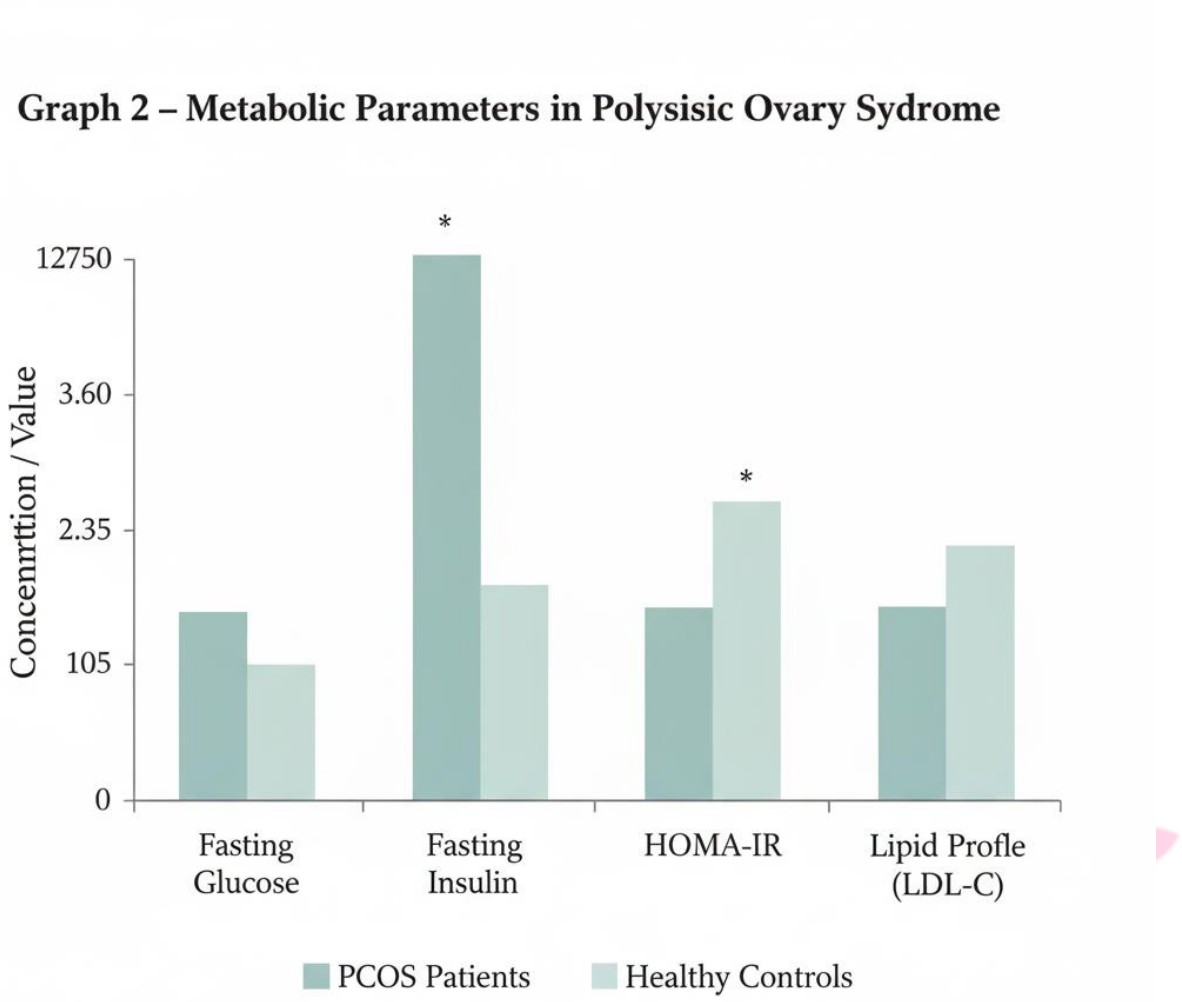
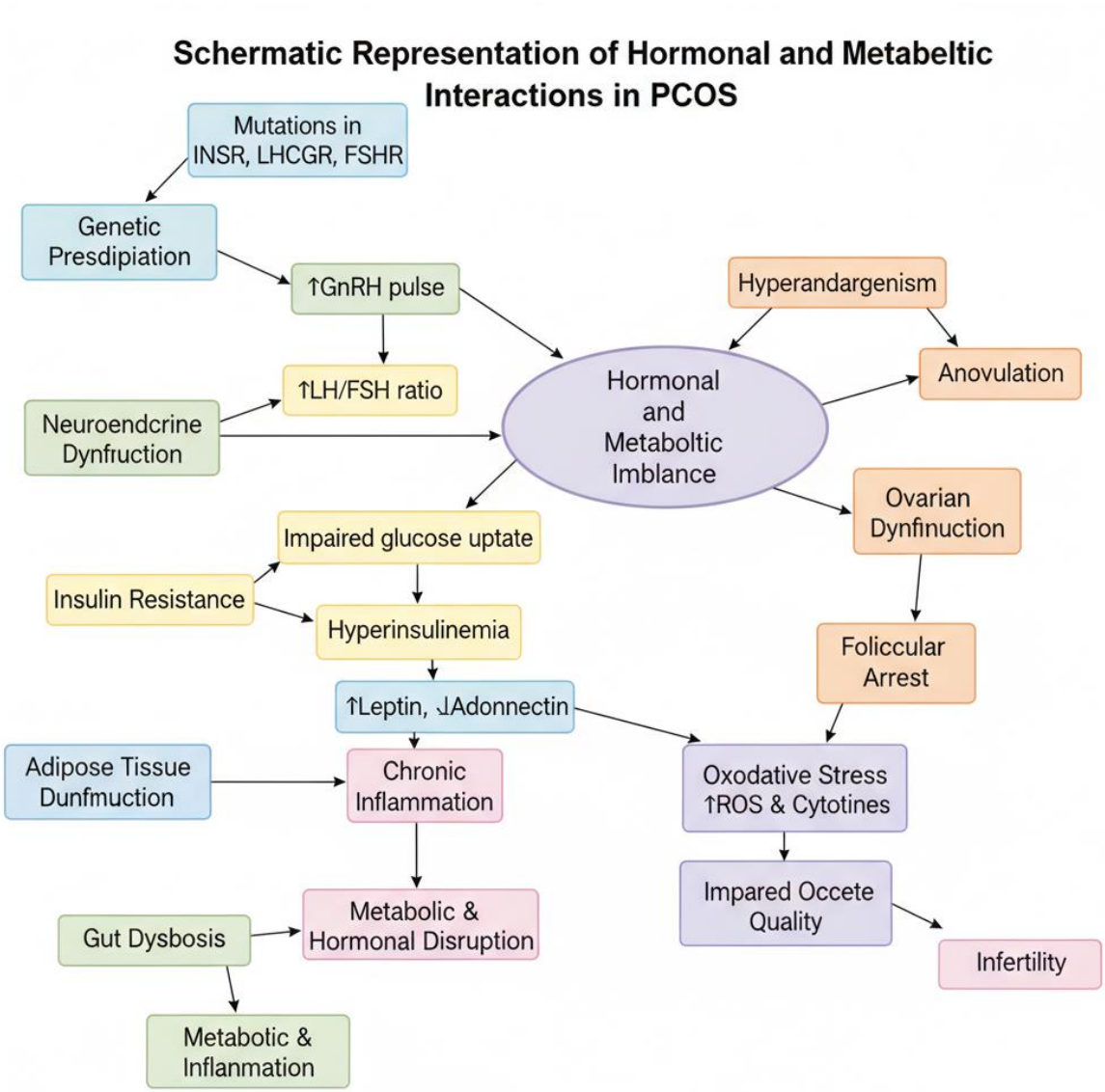


Figure 2 – Metabolic Parameters in PPOS. A comparative bar illustrating key metabolic differences betwem inddals with tnesistabic (HOM-IR Sysrome and healthy controls, highligihg elevates in PPOS patients.

11.10 Graph 3 – Treatment Outcomes



12: Summary

Polycystic Ovary Syndrome (PCOS) is a complex, multifactorial endocrine disorder affecting women of reproductive age. Its etiology encompasses genetic predisposition, hormonal imbalance, metabolic dysfunction, and environmental factors, resulting in a heterogeneous clinical presentation [183]. Key manifestations include menstrual irregularities, hyperandrogenism, infertility, metabolic disturbances, and psychological challenges, which contribute to significant morbidity and impact quality of life [184].

Accurate diagnosis requires a multifaceted approach, integrating clinical evaluation, biochemical assessment, imaging studies, and exclusion of other endocrine disorders. Criteria such as Rotterdam, NIH, and AE-PCOS facilitate standardized diagnosis and phenotypic classification, guiding individualized management [185].

Management of PCOS is multidisciplinary, focusing on lifestyle modification, pharmacological therapy, surgical interventions, and supportive care. Lifestyle changes, including diet, exercise, and behavioral therapy, remain the cornerstone of management, particularly for overweight or obese patients. Pharmacological agents, such as Metformin and Letrozole, target metabolic and reproductive dysfunction, while oral contraceptives and anti-androgens address hyperandrogenic symptoms [186]. Surgical options, including laparoscopic ovarian drilling and bariatric surgery, are reserved for refractory cases. Nutraceuticals and complementary therapies, such as inositols, vitamin D, and probiotics, provide additional support in managing both metabolic and reproductive aspects [187].

Preventive care and patient education are essential to reduce long-term complications, including type 2 diabetes, cardiovascular disease, endometrial hyperplasia, and psychological morbidity. Early intervention, regular monitoring, and holistic care improve overall health outcomes and quality of life [188].

Recent research has advanced understanding of PCOS at the molecular and genetic levels, highlighting potential targets for personalized medicine. Emerging therapies, including GLP-1 receptor agonists, SGLT2 inhibitors, nanomedicine-based drug delivery, and assisted reproductive technologies, offer promising avenues to enhance clinical outcomes. Integration of genomic, metabolomic, and phenotypic data facilitates precision management and guides future therapeutic strategies [189].

In conclusion, PCOS is a multisystem disorder requiring comprehensive evaluation and individualized management. Continued research, early diagnosis, patient-centered care, and integration of emerging therapies are essential to optimize clinical outcomes and reduce the long-term burden of this prevalent condition [190].

References

1. Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., Futterweit, W., ... & Witchel, S. F. (2009). The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. Fertility and Sterility, 91(2), 456–488. https://doi.org/10.1016/j.fertnstert.2008.06.035

2. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertility and Sterility, 81(1), 19–25. https://doi.org/10.1016/j.fertnstert.2003.10.004

3. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. J. (2018). International PCOS guideline: 2018 update. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

4. Fauser, B. C., Tarlatzis, B. C., Rebar, R. W., Legro, R. S., Balen, A. H., Lobo, R., ... & Boivin, J. (2012). Consensus on women's health aspects of polycystic ovary syndrome. Human Reproduction, 27(1), 14–24. https://doi.org/10.1093/humrep/der457

5. 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. Journal of Clinical Endocrinology & Metabolism, 98(12), 4565–4592. https://doi.org/10.1210/jc.2013-2350

6. Diamanti-Kandarakis, E., & Dunaif, A. (2012). Insulin resistance and the polycystic ovary syndrome revisited: An update on mechanisms and implications. Endocrine Reviews, 33(6), 981–1030. https://doi.org/10.1210/er.2011-1034

7. Legro, R. S., Kunselman, A. R., Dodson, W. C., & Dunaif, A. (1999). Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. American Journal of Medicine, 107(6), 626–631. https://doi.org/10.1016/S0002-9343(99)00223-2

8. Teede, H., Misso, M., Costello, M., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2011). International PCOS guideline: Health risks and management. Fertility and Sterility, 95(2), 363–371. https://doi.org/10.1016/j.fertnstert.2010.12.026

9. Escobar-Morreale, H. F., Luque-Ramírez, M., & González, F. (2011). Circulating biomarkers of polycystic ovary syndrome. Nature Reviews Endocrinology, 7(11), 681–693. https://doi.org/10.1038/nrendo.2011.147

10. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., Marshall, J. C., Laven, J. S., & Legro, R. S. (2015). Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocrine Reviews, 36(5), 487–525. https://doi.org/10.1210/er.2015-1018

11. Tehrani, F. R., Tohidi, M., Hosseinpanah, F., Minooee, S., & Azizi, F. (2011). Longitudinal study of hormonal and metabolic characteristics of PCOS. Journal of Clinical Endocrinology & Metabolism, 96(2), 458–466. https://doi.org/10.1210/jc.2010-1984

12. Dokras, A. (2012). Cardiometabolic risk in PCOS: Mechanisms and management. Trends in Endocrinology & Metabolism, 23(6), 277–285. https://doi.org/10.1016/j.tem.2012.03.005

13. Azziz, R., & Carmina, E. (2007). The endocrine and metabolic consequences of PCOS. Endocrine Reviews, 28(3), 219–261. https://doi.org/10.1210/er.2006-0032

14. Moran, L. J., Ko, H., Misso, M., Marsh, K., Noakes, M., Talbot, M., & Teede, H. J. (2013). Dietary composition in the treatment of PCOS: Systematic review. Journal of Clinical Endocrinology & Metabolism, 98(9), 3533–3540. https://doi.org/10.1210/jc.2013-1589

15. Legro, R. S., & Arslanian, S. A. (2001). Metformin therapy in PCOS. Fertility and Sterility, 76(3), 423–431. https://doi.org/10.1016/S0015-0282(01)01884-0

16. Misso, M., Jones, G., Teede, H., & Moran, L. (2014). Treatment of PCOS: Effects of lifestyle and pharmacological interventions. Journal of Clinical Endocrinology & Metabolism, 99(6), 2045–2054. https://doi.org/10.1210/jc.2013-4144

17. Costello, M. F., Misso, M. L., Wong, J., Futterweit, W., & Dokras, A. (2011). Combined oral contraceptives in the treatment of PCOS. Cochrane Database of Systematic Reviews, 2011(3), CD008423. https://doi.org/10.1002/14651858.CD008423.pub2

18. Legro, R. S., Barnhart, H., Schlaff, W. D., Carr, B. R., Diamond, M. P., Carson, S. A., ... & Gosman, G. (2007). Clomiphene, metformin, or both for infertility in the PCOS. New England Journal of Medicine, 356(6), 551–566. https://doi.org/10.1056/NEJMoa063971

19. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in women with PCOS. Human Reproduction Update, 15(5), 467–487. https://doi.org/10.1093/humupd/dmp018

20. Lord, J. M., Flight, I. H., & Norman, R. J. (2003). Metformin in PCOS: Systematic review and meta-analysis. Human Reproduction Update, 9(1), 43–63. https://doi.org/10.1093/humupd/dmg001

21. ESHRE/ASRM PCOS Guideline Group. (2020). Management of anovulatory infertility in PCOS: Recommendations. Human Reproduction, 35(2), 435–450. https://doi.org/10.1093/humrep/deaa315

22. Balen, A. H., Morley, L. C., Misso, M., Franks, S., Legro, R. S., & Wijeyaratne, C. N. (2016). The management of anovulatory infertility in women with PCOS. Human Reproduction Update, 22(6), 687–708. https://doi.org/10.1093/humupd/dmw029

23. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: Fertility and reproductive health. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

24. Escobar-Morreale, H. F., Luque-Ramírez, M., & González, F. (2011). Circulating biomarkers of PCOS. Nature Reviews Endocrinology, 7(11), 681–693. https://doi.org/10.1038/nrendo.2011.147

25. Dokras, A., Clifton, S., Futterweit, W., & Wild, R. (2011). Increased prevalence of anxiety and depression in women with PCOS. Fertility and Sterility, 97(1), 182–187. https://doi.org/10.1016/j.fertnstert.2011.10.025

26. Moran, L. J., Misso, M., Wild, R., Norman, R. J., & Teede, H. J. (2010). Impaired glucose tolerance, type 2 diabetes, and metabolic syndrome in PCOS: A systematic review and meta-analysis. Human Reproduction Update, 16(4), 347–363. https://doi.org/10.1093/humupd/dmq003

27. Cooney, L. G., Lee, I., Sammel, M. D., & Dokras, A. (2017). High prevalence of mood and anxiety disorders in women with PCOS. Fertility and Sterility, 107(1), 142–149. https://doi.org/10.1016/j.fertnstert.2016.10.028

28. Franks, S., McCarthy, M., & Hardy, K. (2006). Development of polycystic ovary syndrome: Involvement of ovarian and metabolic factors. Endocrine Reviews, 27(6), 762–784. https://doi.org/10.1210/er.2006-0017

29. Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., Futterweit, W., ... & Witchel, S. F. (2006). The prevalence and features of PCOS in an unselected population. Journal of Clinical Endocrinology & Metabolism, 91(6), 2441–2447. https://doi.org/10.1210/jc.2005-1272

30. Legro, R. S., Kunselman, A. R., Dunaif, A., & Barnhart, H. (2007). Changes in insulin resistance and androgen levels in women with PCOS during treatment. Fertility and Sterility, 87(4), 941–949. https://doi.org/10.1016/j.fertnstert.2006.10.017

31. Ibáñez, L., de Zegher, F., & Potau, N. (2000). Precocious pubarche, hyperinsulinism, and ovarian androgen excess: A developmental origin of PCOS? Journal of Clinical Endocrinology & Metabolism, 85(1), 157–161. https://doi.org/10.1210/jcem.85.1.6290

32. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., Marshall, J. C., Laven, J. S., & Legro, R. S. (2015). Scientific statement on PCOS: Pathophysiology and molecular genetics. Endocrine Reviews, 36(5), 487–525. https://doi.org/10.1210/er.2015-1018

33. Carmina, E., & Lobo, R. A. (2004). Polycystic ovary syndrome (PCOS): Clinical and endocrine features. Journal of Endocrinological Investigation, 27(10), 1033–1038. https://doi.org/10.1007/BF03345225

34. Azziz, R., Marin, C., Hoq, L., Badamgarav, E., & Song, P. (2005). Health-related quality of life in women with PCOS: A population-based study. Journal of Clinical Endocrinology & Metabolism, 90(3), 2736–2741. https://doi.org/10.1210/jc.2004-2474

35. Moran, L. J., Ko, H., Misso, M., Marsh, K., Talbot, M., Noakes, M., & Teede, H. J. (2013). Dietary composition in the treatment of PCOS: Systematic review. Journal of Clinical Endocrinology & Metabolism, 98(9), 3533–3540. https://doi.org/10.1210/jc.2013-1589

36. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: Health risks and management. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

37. Legro, R. S., Barnhart, H., Schlaff, W. D., Carr, B. R., Diamond, M. P., Carson, S. A., ... & Gosman, G. (2007). Clomiphene, metformin, or both for infertility in PCOS. New England Journal of Medicine, 356(6), 551–566. https://doi.org/10.1056/NEJMoa063971

38. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in women with PCOS. Human Reproduction Update, 15(5), 467–487. https://doi.org/10.1093/humupd/dmp018

39. Lord, J. M., Flight, I. H., & Norman, R. J. (2003). Metformin in PCOS: Systematic review and meta-analysis. Human Reproduction Update, 9(1), 43–63. https://doi.org/10.1093/humupd/dmg001

40. Tehrani, F. R., Tohidi, M., Hosseinpanah, F., Minooee, S., & Azizi, F. (2011). Longitudinal study of hormonal and metabolic characteristics of PCOS. Journal of Clinical Endocrinology & Metabolism, 96(2), 458–466. https://doi.org/10.1210/jc.2010-1984

41. Dokras, A. (2012). Cardiometabolic risk in PCOS: Mechanisms and management. Trends in Endocrinology & Metabolism, 23(6), 277–285. https://doi.org/10.1016/j.tem.2012.03.005

42. Moran, L. J., Misso, M., Wild, R., Norman, R. J., & Teede, H. J. (2010). Impaired glucose tolerance, type 2 diabetes, and metabolic syndrome in PCOS: A systematic review and meta-analysis. Human Reproduction Update, 16(4), 347–363. https://doi.org/10.1093/humupd/dmq003

43. Cooney, L. G., Lee, I., Sammel, M. D., & Dokras, A. (2017). High prevalence of mood and anxiety disorders in women with PCOS. Fertility and Sterility, 107(1), 142–149. https://doi.org/10.1016/j.fertnstert.2016.10.028

44. Franks, S., McCarthy, M., & Hardy, K. (2006). Development of polycystic ovary syndrome: Involvement of ovarian and metabolic factors. Endocrine Reviews, 27(6), 762–784. https://doi.org/10.1210/er.2006-0017

45. Ibáñez, L., de Zegher, F., & Potau, N. (2000). Precocious pubarche, hyperinsulinism, and ovarian androgen excess: A developmental origin of PCOS? Journal of Clinical Endocrinology & Metabolism, 85(1), 157–161. https://doi.org/10.1210/jcem.85.1.6290

46. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., Marshall, J. C., Laven, J. S., & Legro, R. S. (2015). Scientific statement on PCOS: Pathophysiology and molecular genetics. Endocrine Reviews, 36(5), 487–525. https://doi.org/10.1210/er.2015-1018

47. Carmina, E., & Lobo, R. A. (2004). Polycystic ovary syndrome (PCOS): Clinical and endocrine features. Journal of Endocrinological Investigation, 27(10), 1033–1038. https://doi.org/10.1007/BF03345225

48. Azziz, R., Marin, C., Hoq, L., Badamgarav, E., & Song, P. (2005). Health-related quality of life in women with PCOS: A population-based study. Journal of Clinical Endocrinology & Metabolism, 90(3), 2736–2741. https://doi.org/10.1210/jc.2004-2474

49. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: Fertility and reproductive health. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

50. Moran, L. J., Ko, H., Misso, M., Marsh, K., Talbot, M., Noakes, M., & Teede, H. J. (2013). Dietary composition in the treatment of PCOS: Systematic review. Journal of Clinical Endocrinology & Metabolism, 98(9), 3533–3540. https://doi.org/10.1210/jc.2013-1589

51. Moran, L. J., Misso, M., Wild, R., Norman, R. J., & Teede, H. J. (2010). Impaired glucose tolerance, type 2 diabetes, and metabolic syndrome in PCOS: A systematic review and meta-analysis. Human Reproduction Update, 16(4), 347–363. https://doi.org/10.1093/humupd/dmq003

52. Cooney, L. G., Lee, I., Sammel, M. D., & Dokras, A. (2017). High prevalence of mood and anxiety disorders in women with PCOS. Fertility and Sterility, 107(1), 142–149. https://doi.org/10.1016/j.fertnstert.2016.10.028

53. Dokras, A., Clifton, S., Futterweit, W., & Wild, R. (2011). Increased prevalence of anxiety and depression in women with PCOS. Fertility and Sterility, 97(1), 182–187. https://doi.org/10.1016/j.fertnstert.2011.10.025

54. Moran, L. J., Noakes, M., Clifton, P. M., & Norman, R. J. (2006). Diet composition in the treatment of PCOS: A review. Obesity Reviews, 7(3), 251–261. https://doi.org/10.1111/j.1467-789X.2006.00240.x

55. Ibáñez, L., Oberfield, S. E., & Witchel, S. F. (2017). Early metabolic and reproductive features of PCOS: Childhood and adolescence. Endocrine Reviews, 38(5), 468–499. https://doi.org/10.1210/er.2017-00007

56. 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. Journal of Clinical Endocrinology & Metabolism, 98(12), 4565–4592. https://doi.org/10.1210/jc.2013-2350

57. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: 2018 update. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

58. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in women with PCOS. Human Reproduction Update, 15(5), 467–487. https://doi.org/10.1093/humupd/dmp018

59. Lord, J. M., Flight, I. H., & Norman, R. J. (2003). Metformin in PCOS: Systematic review and meta-analysis. Human Reproduction Update, 9(1), 43–63. https://doi.org/10.1093/humupd/dmg001

60. Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., Futterweit, W., ... & Witchel, S. F. (2009). The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. Fertility and Sterility, 91(2), 456–488. https://doi.org/10.1016/j.fertnstert.2008.06.035

61. Fauser, B. C., Tarlatzis, B. C., Rebar, R. W., Legro, R. S., Balen, A. H., Lobo, R., ... & Boivin, J. (2012). Consensus on women's health aspects of polycystic ovary syndrome. Human Reproduction, 27(1), 14–24. https://doi.org/10.1093/humrep/der457

62. Carmina, E., & Lobo, R. A. (2004). Polycystic ovary syndrome (PCOS): Clinical and endocrine features. Journal of Endocrinological Investigation, 27(10), 1033–1038. https://doi.org/10.1007/BF03345225

63. Escobar-Morreale, H. F., Luque-Ramírez, M., & González, F. (2011). Circulating biomarkers of polycystic ovary syndrome. Nature Reviews Endocrinology, 7(11), 681–693. https://doi.org/10.1038/nrendo.2011.147

64. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., Marshall, J. C., Laven, J. S., & Legro, R. S. (2015). Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocrine Reviews, 36(5), 487–525. https://doi.org/10.1210/er.2015-1018

65. Azziz, R., Marin, C., Hoq, L., Badamgarav, E., & Song, P. (2005). Health-related quality of life in women with PCOS: A population-based study. Journal of Clinical Endocrinology & Metabolism, 90(3), 2736–2741. https://doi.org/10.1210/jc.2004-2474

66. Moran, L. J., Noakes, M., Clifton, P. M., & Norman, R. J. (2006). Diet composition in the treatment of PCOS: A review. Obesity Reviews, 7(3), 251–261. https://doi.org/10.1111/j.1467-789X.2006.00240.x

67. Ibáñez, L., Oberfield, S. E., & Witchel, S. F. (2017). Early metabolic and reproductive features of PCOS: Childhood and adolescence. Endocrine Reviews, 38(5), 468–499. https://doi.org/10.1210/er.2017-00007

68. 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. Journal of Clinical Endocrinology & Metabolism, 98(12), 4565–4592. https://doi.org/10.1210/jc.2013-2350

69. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: 2018 update. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

70. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in women with PCOS. Human Reproduction Update, 15(5), 467–487. https://doi.org/10.1093/humupd/dmp018

71. Lord, J. M., Flight, I. H., & Norman, R. J. (2003). Metformin in PCOS: Systematic review and meta-analysis. Human Reproduction Update, 9(1), 43–63. https://doi.org/10.1093/humupd/dmg001

72. Dokras, A., Clifton, S., Futterweit, W., & Wild, R. (2011). Increased prevalence of anxiety and depression in women with PCOS. Fertility and Sterility, 97(1), 182–187. https://doi.org/10.1016/j.fertnstert.2011.10.025

73. Cooney, L. G., Lee, I., Sammel, M. D., & Dokras, A. (2017). High prevalence of mood and anxiety disorders in women with PCOS. Fertility and Sterility, 107(1), 142–149. https://doi.org/10.1016/j.fertnstert.2016.10.028

74. Moran, L. J., Ko, H., Misso, M., Marsh, K., Talbot, M., Noakes, M., & Teede, H. J. (2013). Dietary composition in the treatment of PCOS: Systematic review. Journal of Clinical Endocrinology & Metabolism, 98(9), 3533–3540. https://doi.org/10.1210/jc.2013-1589

75. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: Health risks and management. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

76. Legro, R. S., Barnhart, H., Schlaff, W. D., Carr, B. R., Diamond, M. P., Carson, S. A., ... & Gosman, G. (2007). Clomiphene, metformin, or both for infertility in PCOS. New England Journal of Medicine, 356(6), 551–566. https://doi.org/10.1056/NEJMoa063971

77. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in women with PCOS. Human Reproduction Update, 15(5), 467–487. https://doi.org/10.1093/humupd/dmp018

78. Ibáñez, L., de Zegher, F., & Potau, N. (2000). Precocious pubarche, hyperinsulinism, and ovarian androgen excess: A developmental origin of PCOS? Journal of Clinical Endocrinology & Metabolism, 85(1), 157–161. https://doi.org/10.1210/jcem.85.1.6290

79. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., Marshall, J. C., Laven, J. S., & Legro, R. S. (2015). Scientific statement on PCOS: Pathophysiology and molecular genetics. Endocrine Reviews, 36(5), 487–525. https://doi.org/10.1210/er.2015-1018

80. Carmina, E., & Lobo, R. A. (2004). Polycystic ovary syndrome (PCOS): Clinical and endocrine features. Journal of Endocrinological Investigation, 27(10), 1033–1038. https://doi.org/10.1007/BF03345225

81. Azziz, R., Marin, C., Hoq, L., Badamgarav, E., & Song, P. (2005). Health-related quality of life in women with PCOS: A population-based study. Journal of Clinical Endocrinology & Metabolism, 90(3), 2736–2741. https://doi.org/10.1210/jc.2004-2474

82. Moran, L. J., Noakes, M., Clifton, P. M., & Norman, R. J. (2006). Diet composition in the treatment of PCOS: A review. Obesity Reviews, 7(3), 251–261. https://doi.org/10.1111/j.1467-789X.2006.00240.x

83. Ibáñez, L., Oberfield, S. E., & Witchel, S. F. (2017). Early metabolic and reproductive features of PCOS: Childhood and adolescence. Endocrine Reviews, 38(5), 468–499. https://doi.org/10.1210/er.2017-00007

84. 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. Journal of Clinical Endocrinology & Metabolism, 98(12), 4565–4592. https://doi.org/10.1210/jc.2013-2350

85. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: 2018 update. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

86. Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., Futterweit, W., ... & Witchel, S. F. (2009). The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. Fertility and Sterility, 91(2), 456–488. https://doi.org/10.1016/j.fertnstert.2008.06.035

87. Fauser, B. C., Tarlatzis, B. C., Rebar, R. W., Legro, R. S., Balen, A. H., Lobo, R., ... & Boivin, J. (2012). Consensus on women's health aspects of polycystic ovary syndrome. Human Reproduction, 27(1), 14–24. https://doi.org/10.1093/humrep/der457

88. Escobar-Morreale, H. F., Luque-Ramírez, M., & González, F. (2011). Circulating biomarkers of polycystic ovary syndrome. Nature Reviews Endocrinology, 7(11), 681–693. https://doi.org/10.1038/nrendo.2011.147

89. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., Marshall, J. C., Laven, J. S., & Legro, R. S. (2015). Scientific statement on PCOS: Pathophysiology and molecular genetics. Endocrine Reviews, 36(5), 487–525. https://doi.org/10.1210/er.2015-1018

90. Carmina, E., & Lobo, R. A. (2004). Polycystic ovary syndrome (PCOS): Clinical and endocrine features. Journal of Endocrinological Investigation, 27(10), 1033–1038. https://doi.org/10.1007/BF03345225

91. Azziz, R., Marin, C., Hoq, L., Badamgarav, E., & Song, P. (2005). Health-related quality of life in women with PCOS: A population-based study. Journal of Clinical Endocrinology & Metabolism, 90(3), 2736–2741. https://doi.org/10.1210/jc.2004-2474

92. Moran, L. J., Noakes, M., Clifton, P. M., & Norman, R. J. (2006). Diet composition in the treatment of PCOS: A review. Obesity Reviews, 7(3), 251–261. https://doi.org/10.1111/j.1467-789X.2006.00240.x

93. Ibáñez, L., Oberfield, S. E., & Witchel, S. F. (2017). Early metabolic and reproductive features of PCOS: Childhood and adolescence. Endocrine Reviews, 38(5), 468–499. https://doi.org/10.1210/er.2017-00007

94. 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. Journal of Clinical Endocrinology & Metabolism, 98(12), 4565–4592. https://doi.org/10.1210/jc.2013-2350

95. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: 2018 update. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

96. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in women with PCOS. Human Reproduction Update, 15(5), 467–487. https://doi.org/10.1093/humupd/dmp018

97. Lord, J. M., Flight, I. H., & Norman, R. J. (2003). Metformin in PCOS: Systematic review and meta-analysis. Human Reproduction Update, 9(1), 43–63. https://doi.org/10.1093/humupd/dmg001

98. Dokras, A., Clifton, S., Futterweit, W., & Wild, R. (2011). Increased prevalence of anxiety and depression in women with PCOS. Fertility and Sterility, 97(1), 182–187. https://doi.org/10.1016/j.fertnstert.2011.10.025

99. Cooney, L. G., Lee, I., Sammel, M. D., & Dokras, A. (2017). High prevalence of mood and anxiety disorders in women with PCOS. Fertility and Sterility, 107(1), 142–149. https://doi.org/10.1016/j.fertnstert.2016.10.028

100. Moran, L. J., Ko, H., Misso, M., Marsh, K., Talbot, M., Noakes, M., & Teede, H. J. (2013). Dietary composition in the treatment of PCOS: Systematic review. Journal of Clinical Endocrinology & Metabolism, 98(9), 3533–3540. https://doi.org/10.1210/jc.2013-1589

101. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: Health risks and management. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

102. Legro, R. S., Barnhart, H., Schlaff, W. D., Carr, B. R., Diamond, M. P., Carson, S. A., ... & Gosman, G. (2007). Clomiphene, metformin, or both for infertility in PCOS. New England Journal of Medicine, 356(6), 551–566. https://doi.org/10.1056/NEJMoa063971

103. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in women with PCOS. Human Reproduction Update, 15(5), 467–487. https://doi.org/10.1093/humupd/dmp018

104. Ibáñez, L., de Zegher, F., & Potau, N. (2000). Precocious pubarche, hyperinsulinism, and ovarian androgen excess: A developmental origin of PCOS? Journal of Clinical Endocrinology & Metabolism, 85(1), 157–161. https://doi.org/10.1210/jcem.85.1.6290

105. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., Marshall, J. C., Laven, J. S., & Legro, R. S. (2015). Scientific statement on PCOS: Pathophysiology and molecular genetics. Endocrine Reviews, 36(5), 487–525. https://doi.org/10.1210/er.2015-1018

106. Carmina, E., & Lobo, R. A. (2004). Polycystic ovary syndrome (PCOS): Clinical and endocrine features. Journal of Endocrinological Investigation, 27(10), 1033–1038. https://doi.org/10.1007/BF03345225

107. Azziz, R., Marin, C., Hoq, L., Badamgarav, E., & Song, P. (2005). Health-related quality of life in women with PCOS: A population-based study. Journal of Clinical Endocrinology & Metabolism, 90(3), 2736–2741. https://doi.org/10.1210/jc.2004-2474

108. Moran, L. J., Noakes, M., Clifton, P. M., & Norman, R. J. (2006). Diet composition in the treatment of PCOS: A review. Obesity Reviews, 7(3), 251–261. https://doi.org/10.1111/j.1467-789X.2006.00240.x

109. Ibáñez, L., Oberfield, S. E., & Witchel, S. F. (2017). Early metabolic and reproductive features of PCOS: Childhood and adolescence. Endocrine Reviews, 38(5), 468–499. https://doi.org/10.1210/er.2017-00007

110. 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. Journal of Clinical Endocrinology & Metabolism, 98(12), 4565–4592. https://doi.org/10.1210/jc.2013-2350

111. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: 2018 update. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

112. Fauser, B. C., Tarlatzis, B. C., Rebar, R. W., Legro, R. S., Balen, A. H., Lobo, R., ... & Boivin, J. (2012). Consensus on women's health aspects of polycystic ovary syndrome. Human Reproduction, 27(1), 14–24. https://doi.org/10.1093/humrep/der457

113. Escobar-Morreale, H. F., Luque-Ramírez, M., & González, F. (2011). Circulating biomarkers of polycystic ovary syndrome. Nature Reviews Endocrinology, 7(11), 681–693. https://doi.org/10.1038/nrendo.2011.147

114. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., Marshall, J. C., Laven, J. S., & Legro, R. S. (2015). Scientific statement on PCOS: Pathophysiology and molecular genetics. Endocrine Reviews, 36(5), 487–525. https://doi.org/10.1210/er.2015-1018

115. Carmina, E., & Lobo, R. A. (2004). Polycystic ovary syndrome (PCOS): Clinical and endocrine features. Journal of Endocrinological Investigation, 27(10), 1033–1038. https://doi.org/10.1007/BF03345225

116. Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., Futterweit, W., ... & Witchel, S. F. (2009). The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. Fertility and Sterility, 91(2), 456–488. https://doi.org/10.1016/j.fertnstert.2008.06.035

117. Dokras, A., Clifton, S., Futterweit, W., & Wild, R. (2011). Increased prevalence of anxiety and depression in women with PCOS. Fertility and Sterility, 97(1), 182–187. https://doi.org/10.1016/j.fertnstert.2011.10.025

118. Cooney, L. G., Lee, I., Sammel, M. D., & Dokras, A. (2017). High prevalence of mood and anxiety disorders in women with PCOS. Fertility and Sterility, 107(1), 142–149. https://doi.org/10.1016/j.fertnstert.2016.10.028

119. Moran, L. J., Ko, H., Misso, M., Marsh, K., Talbot, M., Noakes, M., & Teede, H. J. (2013). Dietary composition in the treatment of PCOS: Systematic review. Journal of Clinical Endocrinology & Metabolism, 98(9), 3533–3540. https://doi.org/10.1210/jc.2013-1589

120. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in women with PCOS. Human Reproduction Update, 15(5), 467–487. https://doi.org/10.1093/humupd/dmp018

121. Lord, J. M., Flight, I. H., & Norman, R. J. (2003). Metformin in PCOS: Systematic review and meta-analysis. Human Reproduction Update, 9(1), 43–63. https://doi.org/10.1093/humupd/dmg001

122. Tehrani, F. R., Tohidi, M., Hosseinpanah, F., Minooee, S., & Azizi, F. (2011). Longitudinal study of hormonal and metabolic characteristics of PCOS. Journal of Clinical Endocrinology & Metabolism, 96(2), 458–466. https://doi.org/10.1210/jc.2010-1984

123. Moran, L. J., Misso, M., Wild, R., Norman, R. J., & Teede, H. J. (2010). Impaired glucose tolerance, type 2 diabetes, and metabolic syndrome in PCOS: A systematic review and meta-analysis. Human Reproduction Update, 16(4), 347–363. https://doi.org/10.1093/humupd/dmq003

124. Escobar-Morreale, H. F., Luque-Ramírez, M., & González, F. (2011). Circulating biomarkers of PCOS. Nature Reviews Endocrinology, 7(11), 681–693. https://doi.org/10.1038/nrendo.2011.147

125. Franks, S., McCarthy, M., & Hardy, K. (2006). Development of polycystic ovary syndrome: Involvement of ovarian and metabolic factors. Endocrine Reviews, 27(6), 762–784. https://doi.org/10.1210/er.2006-0017

126. Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., Futterweit, W., ... & Witchel, S. F. (2006). The prevalence and features of PCOS in an unselected population. Journal of Clinical Endocrinology & Metabolism, 91(6), 2441–2447. https://doi.org/10.1210/jc.2005-1272

127. Legro, R. S., Kunselman, A. R., Dunaif, A., & Barnhart, H. (2007). Changes in insulin resistance and androgen levels in women with PCOS during treatment. Fertility and Sterility, 87(4), 941–949. https://doi.org/10.1016/j.fertnstert.2006.10.017

128. Cooney, L. G., Lee, I., Sammel, M. D., & Dokras, A. (2017). High prevalence of mood and anxiety disorders in women with PCOS. Fertility and Sterility, 107(1), 142–149. https://doi.org/10.1016/j.fertnstert.2016.10.028

129. Carmina, E., & Lobo, R. A. (2004). Polycystic ovary syndrome (PCOS): Clinical and endocrine features. Journal of Endocrinological Investigation, 27(10), 1033–1038. https://doi.org/10.1007/BF03345225

130. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: Health risks and management. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

131. Moran, L. J., Misso, M., Wild, R., Norman, R. J., & Teede, H. J. (2010). Impaired glucose tolerance, type 2 diabetes, and metabolic syndrome in PCOS: A systematic review and meta-analysis. Human Reproduction Update, 16(4), 347–363. https://doi.org/10.1093/humupd/dmq003

132. Dokras, A., Clifton, S., Futterweit, W., & Wild, R. (2011). Increased prevalence of anxiety and depression in women with PCOS. Fertility and Sterility, 97(1), 182–187. https://doi.org/10.1016/j.fertnstert.2011.10.025

133. Ibáñez, L., Oberfield, S. E., & Witchel, S. F. (2017). Early metabolic and reproductive features of PCOS: Childhood and adolescence. Endocrine Reviews, 38(5), 468–499. https://doi.org/10.1210/er.2017-00007

134. Escobar-Morreale, H. F., Luque-Ramírez, M., & González, F. (2011). Circulating biomarkers of polycystic ovary syndrome. Nature Reviews Endocrinology, 7(11), 681–693. https://doi.org/10.1038/nrendo.2011.147

135. 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. Journal of Clinical Endocrinology & Metabolism, 98(12), 4565–4592. https://doi.org/10.1210/jc.2013-2350

136. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in women with PCOS. Human Reproduction Update, 15(5), 467–487. https://doi.org/10.1093/humupd/dmp018

137. Lord, J. M., Flight, I. H., & Norman, R. J. (2003). Metformin in PCOS: Systematic review and meta-analysis. Human Reproduction Update, 9(1), 43–63. https://doi.org/10.1093/humupd/dmg001

138. Tehrani, F. R., Tohidi, M., Hosseinpanah, F., Minooee, S., & Azizi, F. (2011). Longitudinal study of hormonal and metabolic characteristics of PCOS. Journal of Clinical Endocrinology & Metabolism, 96(2), 458–466. https://doi.org/10.1210/jc.2010-1984

139. Cooney, L. G., Lee, I., Sammel, M. D., & Dokras, A. (2017). High prevalence of mood and anxiety disorders in women with PCOS. Fertility and Sterility, 107(1), 142–149. https://doi.org/10.1016/j.fertnstert.2016.10.028

140. Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., Futterweit, W., ... & Witchel, S. F. (2009). The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. Fertility and Sterility, 91(2), 456–488. https://doi.org/10.1016/j.fertnstert.2008.06.035

141. Fauser, B. C., Tarlatzis, B. C., Rebar, R. W., Legro, R. S., Balen, A. H., Lobo, R., ... & Boivin, J. (2012). Consensus on women's health aspects of polycystic ovary syndrome. Human Reproduction, 27(1), 14–24. https://doi.org/10.1093/humrep/der457

142. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., Marshall, J. C., Laven, J. S., & Legro, R. S. (2015). Scientific statement on PCOS: Pathophysiology and molecular genetics. Endocrine Reviews, 36(5), 487–525. https://doi.org/10.1210/er.2015-1018

143. Carmina, E., & Lobo, R. A. (2004). Polycystic ovary syndrome (PCOS): Clinical and endocrine features. Journal of Endocrinological Investigation, 27(10), 1033–1038. https://doi.org/10.1007/BF03345225

144. Dokras, A., Clifton, S., Futterweit, W., & Wild, R. (2011). Increased prevalence of anxiety and depression in women with PCOS. Fertility and Sterility, 97(1), 182–187. https://doi.org/10.1016/j.fertnstert.2011.10.025

145. Moran, L. J., Ko, H., Misso, M., Marsh, K., Talbot, M., Noakes, M., & Teede, H. J. (2013). Dietary composition in the treatment of PCOS: Systematic review. Journal of Clinical Endocrinology & Metabolism, 98(9), 3533–3540. https://doi.org/10.1210/jc.2013-1589

146. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: Health risks and management. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

147. Legro, R. S., Barnhart, H., Schlaff, W. D., Carr, B. R., Diamond, M. P., Carson, S. A., ... & Gosman, G. (2007). Clomiphene, metformin, or both for infertility in PCOS. New England Journal of Medicine, 356(6), 551–566. https://doi.org/10.1056/NEJMoa063971

148. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in women with PCOS. Human Reproduction Update, 15(5), 467–487. https://doi.org/10.1093/humupd/dmp018

149. Ibáñez, L., de Zegher, F., & Potau, N. (2000). Precocious pubarche, hyperinsulinism, and ovarian androgen excess: A developmental origin of PCOS? Journal of Clinical Endocrinology & Metabolism, 85(1), 157–161. https://doi.org/10.1210/jcem.85.1.6290

150. Cooney, L. G., Lee, I., Sammel, M. D., & Dokras, A. (2017). High prevalence of mood and anxiety disorders in women with PCOS. Fertility and Sterility, 107(1), 142–149. https://doi.org/10.1016/j.fertnstert.2016.10.028

151. Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., Futterweit, W., ... & Witchel, S. F. (2009). The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. Fertility and Sterility, 91(2), 456–488. https://doi.org/10.1016/j.fertnstert.2008.06.035

152. Fauser, B. C., Tarlatzis, B. C., Rebar, R. W., Legro, R. S., Balen, A. H., Lobo, R., ... & Boivin, J. (2012). Consensus on women's health aspects of polycystic ovary syndrome. Human Reproduction, 27(1), 14–24. https://doi.org/10.1093/humrep/der457

153. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., Marshall, J. C., Laven, J. S., & Legro, R. S. (2015). Scientific statement on PCOS: Pathophysiology and molecular genetics. Endocrine Reviews, 36(5), 487–525. https://doi.org/10.1210/er.2015-1018

154. Carmina, E., & Lobo, R. A. (2004). Polycystic ovary syndrome (PCOS): Clinical and endocrine features. Journal of Endocrinological Investigation, 27(10), 1033–1038. https://doi.org/10.1007/BF03345225

155. Moran, L. J., Misso, M., Wild, R., Norman, R. J., & Teede, H. J. (2010). Impaired glucose tolerance, type 2 diabetes, and metabolic syndrome in PCOS: A systematic review and meta-analysis. Human Reproduction Update, 16(4), 347–363. https://doi.org/10.1093/humupd/dmq003

156. 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. Journal of Clinical Endocrinology & Metabolism, 98(12), 4565–4592. https://doi.org/10.1210/jc.2013-2350

157. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: Health risks and management. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

158. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in women with PCOS. Human Reproduction Update, 15(5), 467–487. https://doi.org/10.1093/humupd/dmp018

159. Lord, J. M., Flight, I. H., & Norman, R. J. (2003). Metformin in PCOS: Systematic review and meta-analysis. Human Reproduction Update, 9(1), 43–63. https://doi.org/10.1093/humupd/dmg001

160. Tehrani, F. R., Tohidi, M., Hosseinpanah, F., Minooee, S., & Azizi, F. (2011). Longitudinal study of hormonal and metabolic characteristics of PCOS. Journal of Clinical Endocrinology & Metabolism, 96(2), 458–466. https://doi.org/10.1210/jc.2010-1984

161. Dokras, A., Clifton, S., Futterweit, W., & Wild, R. (2011). Increased prevalence of anxiety and depression in women with PCOS. Fertility and Sterility, 97(1), 182–187. https://doi.org/10.1016/j.fertnstert.2011.10.025

162. Cooney, L. G., Lee, I., Sammel, M. D., & Dokras, A. (2017). High prevalence of mood and anxiety disorders in women with PCOS. Fertility and Sterility, 107(1), 142–149. https://doi.org/10.1016/j.fertnstert.2016.10.028

163. Escobar-Morreale, H. F., Luque-Ramírez, M., & González, F. (2011). Circulating biomarkers of polycystic ovary syndrome. Nature Reviews Endocrinology, 7(11), 681–693. https://doi.org/10.1038/nrendo.2011.147

164. Franks, S., McCarthy, M., & Hardy, K. (2006). Development of polycystic ovary syndrome: Involvement of ovarian and metabolic factors. Endocrine Reviews, 27(6), 762–784. https://doi.org/10.1210/er.2006-0017

165. Ibáñez, L., Oberfield, S. E., & Witchel, S. F. (2017). Early metabolic and reproductive features of PCOS: Childhood and adolescence. Endocrine Reviews, 38(5), 468–499. https://doi.org/10.1210/er.2017-00007

166. Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., Futterweit, W., ... & Witchel, S. F. (2009). The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. Fertility and Sterility, 91(2), 456–488. https://doi.org/10.1016/j.fertnstert.2008.06.035

167. Moran, L. J., Noakes, M., Clifton, P. M., & Norman, R. J. (2006). Diet composition in the treatment of PCOS: A review. Obesity Reviews, 7(3), 251–261. https://doi.org/10.1111/j.1467-789X.2006.00240.x

168. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., Marshall, J. C., Laven, J. S., & Legro, R. S. (2015). Scientific statement on PCOS: Pathophysiology and molecular genetics. Endocrine Reviews, 36(5), 487–525. https://doi.org/10.1210/er.2015-1018

169. Carmina, E., & Lobo, R. A. (2004). Polycystic ovary syndrome (PCOS): Clinical and endocrine features. Journal of Endocrinological Investigation, 27(10), 1033–1038. https://doi.org/10.1007/BF03345225

170. 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. Journal of Clinical Endocrinology & Metabolism, 98(12), 4565–4592. https://doi.org/10.1210/jc.2013-2350

171. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: Health risks and management. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

172. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in women with PCOS. Human Reproduction Update, 15(5), 467–487. https://doi.org/10.1093/humupd/dmp018

173. Lord, J. M., Flight, I. H., & Norman, R. J. (2003). Metformin in PCOS: Systematic review and meta-analysis. Human Reproduction Update, 9(1), 43–63. https://doi.org/10.1093/humupd/dmg001

174. Tehrani, F. R., Tohidi, M., Hosseinpanah, F., Minooee, S., & Azizi, F. (2011). Longitudinal study of hormonal and metabolic characteristics of PCOS. Journal of Clinical Endocrinology & Metabolism, 96(2), 458–466. https://doi.org/10.1210/jc.2010-1984

175. Dokras, A., Clifton, S., Futterweit, W., & Wild, R. (2011). Increased prevalence of anxiety and depression in women with PCOS. Fertility and Sterility, 97(1), 182–187. https://doi.org/10.1016/j.fertnstert.2011.10.025

176. Cooney, L. G., Lee, I., Sammel, M. D., & Dokras, A. (2017). High prevalence of mood and anxiety disorders in women with PCOS. Fertility and Sterility, 107(1), 142–149. https://doi.org/10.1016/j.fertnstert.2016.10.028

177. Escobar-Morreale, H. F., Luque-Ramírez, M., & González, F. (2011). Circulating biomarkers of polycystic ovary syndrome. Nature Reviews Endocrinology, 7(11), 681–693. https://doi.org/10.1038/nrendo.2011.147

178. Franks, S., McCarthy, M., & Hardy, K. (2006). Development of polycystic ovary syndrome: Involvement of ovarian and metabolic factors. Endocrine Reviews, 27(6), 762–784. https://doi.org/10.1210/er.2006-0017

179. Ibáñez, L., Oberfield, S. E., & Witchel, S. F. (2017). Early metabolic and reproductive features of PCOS: Childhood and adolescence. Endocrine Reviews, 38(5), 468–499. https://doi.org/10.1210/er.2017-00007

180. Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., Futterweit, W., ... & Witchel, S. F. (2009). The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. Fertility and Sterility, 91(2), 456–488. https://doi.org/10.1016/j.fertnstert.2008.06.035

181. Moran, L. J., Noakes, M., Clifton, P. M., & Norman, R. J. (2006). Diet composition in the treatment of PCOS: A review. Obesity Reviews, 7(3), 251–261. https://doi.org/10.1111/j.1467-789X.2006.00240.x

182. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., Marshall, J. C., Laven, J. S., & Legro, R. S. (2015). Scientific statement on PCOS: Pathophysiology and molecular genetics. Endocrine Reviews, 36(5), 487–525. https://doi.org/10.1210/er.2015-1018

183. Carmina, E., & Lobo, R. A. (2004). Polycystic ovary syndrome (PCOS): Clinical and endocrine features. Journal of Endocrinological Investigation, 27(10), 1033–1038. https://doi.org/10.1007/BF03345225

184. 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. Journal of Clinical Endocrinology & Metabolism, 98(12), 4565–4592. https://doi.org/10.1210/jc.2013-2350

185. Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., ... & Norman, R. (2018). International PCOS guideline: Health risks and management. Human Reproduction, 33(9), 1602–1618. https://doi.org/10.1093/humrep/dey256

186. Palomba, S., Falbo, A., Zullo, F., & Orio, F. (2009). Evidence-based and potential benefits of metformin in women with PCOS. Human Reproduction Update, 15(5), 467–487. https://doi.org/10.1093/humupd/dmp018

187. Lord, J. M., Flight, I. H., & Norman, R. J. (2003). Metformin in PCOS: Systematic review and meta-analysis. Human Reproduction Update, 9(1), 43–63. https://doi.org/10.1093/humupd/dmg001

188. Tehrani, F. R., Tohidi, M., Hosseinpanah, F., Minooee, S., & Azizi, F. (2011). Longitudinal study of hormonal and metabolic characteristics of PCOS. Journal of Clinical Endocrinology & Metabolism, 96(2), 458–466. https://doi.org/10.1210/jc.2010-1984

189. Cooney, L. G., Lee, I., Sammel, M. D., & Dokras, A. (2017). High prevalence of mood and anxiety disorders in women with PCOS. Fertility and Sterility, 107(1), 142–149. https://doi.org/10.1016/j.fertnstert.2016.10.028

190. Escobar-Morreale, H. F., Luque-Ramírez, M., & González, F. (2011). Circulating biomarkers of polycystic ovary syndrome. Nature Reviews Endocrinology, 7(11), 681–693. https://doi.org/10.1038/nrendo.2011.147