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Understanding Polycystic Ovary Syndrome

Symptoms, Diagnosis, and Treatment Options

Edited by Zhengchao Wang

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Meet the Series Editor

Zouhair Amarin is a Professor of Obstetrics and Gynaecology at the Jordan University of Science and Technology. He was previously a lecturer at the University of Glasgow, Scotland, a senior lecturer at the University of Nottingham, England, and the dean of the Faculty of Medicine at Mutah University, Jordan. Professor Amarin is a fellow of the Royal College of Obstetricians and Gynaecologists, and the Faculty of Public Health, London. He holds master's degrees in medical science and medical education. He is a pioneer in IVF and was the first in the world to develop microsurgical epididymis sperm aspiration for clinical use. He also discovered a surgical procedure for critical ovarian hyperstimulation syndrome. Professor Amarin has edited books, authored book chapters, and published more than 130 papers. He is the recipient of eight awards.

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Contents

Preface

Polycystic ovary syndrome (PCOS) is a major health problem. It is a heterogeneous hormone-imbalance disorder that occurs in reproductive-aged women worldwide and is characterized by hyperandrogenism, ovulatory process dysfunction, and polycystic ovaries.

PCOS is influenced by various factors, and there are no unique diagnostic criteria across different regions, due to the heterogeneity of clinical manifestations and endocrine system changes associated with PCOS. Therefore, it is often difficult to accurately diagnose women with PCOS, as the signs and symptoms of PCOS can vary among individuals. Although PCOS is usually diagnosed during the early reproductive years, the precise pathogenesis of PCOS remains unclear. An increasing number of studies have demonstrated that the insulin signaling pathway plays a crucial role in the pathophysiology of PCOS, including phosphatidylinositol 3-kinase and protein kinase B signaling, which are critically implicated in insulin resistance, androgen secretion, obesity, and follicular development. PCOS manifests as defective ovarian steroid biosynthesis and hyperandrogenemia, and 50~70% of women with PCOS exhibit insulin resistance and are hyperinsulinemic, indicating that insulin resistance and hyperinsulinism may have an important role in the pathophysiology of PCOS.

This book offers a comprehensive overview of the current state of the art in PCOS research, benefiting women with PCOS. I hope this book is meaningful to clinicians who care for women with PCOS and to researchers who investigate the complexities of this disease. We sincerely thank all the authors for their contributions to our book.

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Section 1

The Overview of Polycystic Ovary Syndrome

Chapter 1

Understanding Polycystic Ovary Syndrome: A Comprehensive Guide

Omer Tammo

Abstract

Polycystic ovary syndrome (PCOS) stands as a complex and prevalent endocrine disorder, profoundly impacting women throughout their reproductive years. Its hallmark lies in the intricate interplay of hormonal imbalances, primarily characterized by elevated androgen levels, which subsequently trigger a diverse array of clinical manifestations. These manifestations span from disruptive menstrual irregularities, such as oligomenorrhea or amenorrhea, to the visible signs of hyperandrogenism, including hirsutism, acne, and androgenic alopecia. Furthermore, PCOS extends its reach beyond reproductive health, significantly influencing metabolic functions by fostering insulin resistance, thereby escalating the risk of type 2 diabetes, dyslipidemia, and cardiovascular complications. Adding to the syndrome's complexity are the significant psychological ramifications, often leading to increased susceptibility to anxiety, depression, and a diminished sense of self-worth. The diagnostic approach to PCOS hinges on the Rotterdam criteria, which mandates the presence of at least two of the following: oligo- or anovulation, clinical or biochemical evidence of hyperandrogenism, and the characteristic polycystic ovarian morphology as visualized through ultrasound. In terms of management, a multifaceted strategy is imperative, encompassing lifestyle modifications to mitigate insulin resistance, alongside pharmacological interventions tailored to address specific symptoms, such as hormonal therapies to regulate menstruation and antiandrogens to counteract hyperandrogenism. For women grappling with fertility challenges, assisted reproductive technologies offer viable pathways to conception. Thus, a comprehensive and individualized approach, integrating medical, lifestyle, and psychological considerations, is crucial for effectively managing PCOS and enhancing the overall well-being of affected individuals.

Keywords: PCOS, insulin resistance, androgen excess, anovulation, hirsutism

1. Introduction

PCOS is a complex and highly prevalent endocrine disorder that significantly impacts a substantial portion of the female population throughout their reproductive

lifespan; characterized by a complex interplay of hormonal imbalances that result in a triad of key features: irregular menstrual cycles, hyperandrogenism, and the presence of polycystic ovaries [1]. This syndrome not only affects reproductive health but also extends its influence on mental and metabolic well-being, leading to profound consequences on the overall quality of life, necessitating a holistic and multifaceted approach to care. The etiology of PCOS is multifactorial, arising from a complex interplay of genetic predisposition, environmental factors, and disturbances in various endocrine pathways, including insulin resistance, abnormal gonadotropin secretion, and increased ovarian androgen production [2]. This intricate web of factors contributes to the heterogeneous clinical presentation of PCOS and poses significant challenges in both diagnosis and management, leading to significant delays in treatment and increased morbidity.

The diagnostic process is often challenging due to the wide range of symptoms that vary significantly among individuals, influenced by age, ethnicity, and the presence of comorbidities such as obesity, which contributes to diagnostic delays and variability in clinical presentation [3]. For example, studies have indicated that women of certain ethnicities, such as Hispanic and African American women, may present with more severe metabolic manifestations of PCOS, including increased insulin resistance and a higher risk of type 2 diabetes, compared to Caucasian women. Specifically, research has shown that African American women with PCOS have a significantly higher prevalence of metabolic syndrome and are more likely to develop cardiovascular risk factors. Additionally, South Asian women with PCOS often exhibit a higher degree of insulin resistance and are at increased risk for developing type 2 diabetes, even at a lower BMI compared to Caucasian women. These disparities underscore the importance of considering racial and ethnic factors in the diagnostic and management process. Over time, the diagnostic criteria for PCOS have evolved to reflect a more nuanced understanding of the syndrome, with experts now acknowledging that the presence of at least two out of three key features is sufficient for diagnosis, provided that other potential causes of androgen excess and menstrual irregularities, such as congenital adrenal hyperplasia, Cushing's syndrome, and thyroid dysfunction, have been rigorously excluded [4]. This evolution in diagnostic criteria underscores the complexity of PCOS and the need for a comprehensive evaluation that considers the patient's individual presentation, including a thorough medical history, physical examination, and laboratory and imaging studies.

The clinical manifestations of PCOS exert a significant impact on a woman's overall well-being, extending beyond reproductive health to encompass psychological and metabolic dimensions. Irregular menstrual cycles can lead to significant fertility issues, with studies indicating that up to 70–80% of women with PCOS experience infertility due to anovulation, while excess androgen production results in unwanted physical changes such as hirsutism, acne, and weight gain, contributing to emotional distress and a diminished quality of life [5]. Furthermore, PCOS is closely associated with an increased risk of metabolic disorders, including insulin resistance, type 2 diabetes, and cardiovascular disease, with studies showing that women with PCOS are at a three to seven times higher risk of developing type 2 diabetes compared to women without PCOS, and a two to three times higher risk of cardiovascular disease [6]. Studies have also demonstrated that women with PCOS have an increased prevalence of nonalcoholic fatty liver disease (NAFLD) and sleep apnea, further exacerbating their health risks. These metabolic complications further exacerbate the health challenges faced by affected individuals and increase their susceptibility to long-term complications. Despite its relatively high prevalence, with estimates ranging from

6% to 20% of women of reproductive age, the underlying pathophysiology of PCOS remains incompletely understood, necessitating ongoing research to elucidate the precise mechanisms driving hormonal imbalances and metabolic dysfunctions and to identify potential therapeutic targets [2].

The management of PCOS is equally complex, requiring individualized treatment plans that address not only the reproductive and endocrine aspects of the syndrome but also the metabolic and psychological dimensions. Lifestyle modifications, such as weight management and regular exercise, often serve as the first line of defense, aiming to improve insulin sensitivity and reduce androgen levels. Studies have shown that even a 5–10% weight loss can significantly improve menstrual regularity and fertility in women with PCOS. In addition, pharmacological interventions, including oral contraceptives, antiandrogens, and insulin-sensitizing agents, may be necessary to manage specific symptoms or comorbidities and to improve long-term outcomes [1]. Therefore, an interdisciplinary treatment approach, involving endocrinologists, reproductive endocrinologists, dermatologists, psychologists, and nutritionists, is most beneficial to the patient, ensuring comprehensive and coordinated care. This approach must include culturally competent care and be aware of the different rates of diagnosis and symptom presentation in different ethnic groups.

2. Etiology and pathophysiology

PCOS is a complex and highly prevalent endocrine disorder that significantly impacts a substantial portion of women of reproductive age globally, with estimated prevalence rates varying considerably, ranging from 6% to as high as 20%, depending on the population studied [1]. This significant variability underscores the heterogeneous clinical presentations of PCOS across diverse ethnic and geographical groups, highlighting the nuanced influence of genetic and environmental factors on its phenotypic expression and demanding culturally sensitive and population-specific research [7]. The precise etiology of PCOS remains incompletely elucidated, though it is widely accepted that it arises from a sophisticated interplay of genetic predisposition and environmental influences, particularly those occurring during critical phases of fetal or perinatal development, which can increase individual susceptibility to the syndrome [8]. This developmental origins of health and disease (DOHaD) perspective suggests that early-life exposures may program long-term health outcomes, including the development of PCOS.

While the syndrome's historical roots are acknowledged, with suggestions of its existence throughout history, concrete evidence from historical medical records remains elusive, creating an intriguing gap in our understanding of its evolution over time and prompting further investigation into the historical context of endocrine disorders. Contemporary diagnostic approaches to PCOS have evolved substantially, with current clinical practice emphasizing the necessity of fulfilling at least two out of the three Rotterdam criteria—namely, oligo-ovulation and/or anovulation, clinical or biochemical signs of hyperandrogenism, and the presence of polycystic ovaries as visualized by ultrasound—after meticulously excluding other potential etiologies for these symptoms. This stringent diagnostic process is crucial to differentiate PCOS from other endocrine disorders, such as congenital adrenal hyperplasia, thyroid dysfunction, and hyperprolactinemia, which can present with similar symptoms.

The pathophysiology of PCOS is multifaceted and intricate, involving profound disruptions in a variety of endocrine pathways. Genetic factors are paramount, with

accumulating research pointing to the likely involvement of multiple genetic loci and complex gene-environment interactions. Genome-wide association studies (GWAS) have identified several susceptibility loci associated with PCOS, highlighting the polygenic nature of the disorder. Environmental factors, including dietary patterns, levels of physical activity, and exposure to endocrine-disrupting chemicals, also significantly contribute to the development and progression of PCOS [8]. These environmental factors can interact with genetic predispositions to modulate the expression of PCOS, leading to diverse clinical phenotypes.

Despite extensive research, the exact cause of PCOS remains incompletely understood, but it is clear that its pathogenesis is not attributable to a single factor. Central to its pathophysiology is insulin resistance, which often leads to compensatory hyperinsulinemia, thereby stimulating ovarian androgen production. This hormonal milieu disrupts normal follicular development, culminating in anovulation and the characteristic polycystic ovarian morphology detectable through ultrasonography. Insulin resistance is a key driver of metabolic complications associated with PCOS, including type 2 diabetes and cardiovascular disease.

Genetic susceptibility is evidenced by the familial clustering of PCOS cases, while environmental factors such as obesity and sedentary lifestyles can exacerbate insulin resistance, significantly impacting the manifestation and progression of the syndrome [8]. The interplay between genetic and environmental factors underscores the need for personalized approaches to patient management, considering individual risk profiles and lifestyle factors. This integrated understanding of PCOS stresses the complexity of its origins, the spectrum of its clinical expressions, and the necessity of a holistic, patient-centered approach to diagnosis and management, incorporating lifestyle modifications, pharmacological interventions, and psychological support.

3. Clinical manifestations

PCOS presents as a complex and heterogeneous endocrine disorder, significantly impacting women of reproductive age through a cascade of interconnected reproductive, metabolic, and dermatological abnormalities, with a profound influence on overall health and well-being. At its core, PCOS is characterized by chronic anovulation and hyperandrogenism, disrupting normal hormonal balance and leading to a spectrum of clinical manifestations that vary significantly among individuals. These primary features manifest as irregular menstrual cycles, including oligomenorrhea (infrequent menstruation) and amenorrhea (absence of menstruation), significantly impacting fertility and reproductive health, and often leading to distress and diminished quality of life [3, 9]. Beyond reproductive disruptions, PCOS markedly elevates the risk for serious metabolic complications such as type 2 diabetes mellitus, metabolic syndrome, obstructive sleep apnea, and nonalcoholic fatty liver disease, illustrating the systemic and multi-organ involvement of this syndrome and highlighting the need for comprehensive screening and management of these comorbidities [10]. The clinical presentation of PCOS is further complicated by its variability across different racial and ethnic groups, as well as its interaction with obesity, necessitating a nuanced diagnostic approach that integrates comprehensive clinical evaluation with detailed laboratory findings and acknowledges the unique presentations in different populations [7]. For instance, studies have indicated that certain racial and ethnic groups may present with more severe metabolic manifestations of PCOS, such as increased insulin resistance and higher rates of type 2 diabetes,

while others may experience more pronounced dermatological symptoms like hirsutism and acne. Recognizing these differences is crucial for tailoring diagnostic and management strategies to individual patient needs. Common symptoms associated with PCOS include: menstrual irregularities, manifesting as oligomenorrhea, amenorrhea, or irregular menstrual cycles, which are often the initial indicators of hormonal dysregulation and can significantly affect a woman's sense of normalcy and well-being [11]; Hyperandrogenism, resulting in hirsutism (excessive hair growth in a male pattern), acne, and male-pattern alopecia (hair loss), significantly impacting the patient's physical and emotional well-being, and often leading to social anxiety and reduced self-esteem [12]; Polycystic ovaries, characterized by enlarged ovaries containing numerous small follicles arranged around the periphery, creating a "string of pearls" appearance on ultrasound, though this feature alone is not sufficient for diagnosis and must be interpreted in conjunction with other clinical and biochemical findings [13]; Metabolic Dysfunction, primarily characterized by insulin resistance, which increases the risk of type 2 diabetes mellitus, metabolic syndrome, and cardiovascular disease, necessitating proactive management of metabolic risk factors [14]; Obesity, as a significant proportion of women with PCOS are overweight or obese, exacerbating insulin resistance and contributing to the development of other metabolic complications, and emphasizing the importance of weight management as a cornerstone of PCOS treatment [15]; Infertility, with anovulation being a primary cause of infertility among women with PCOS, and often requiring specialized fertility treatments [16]; and psychological impact, as the physical manifestations and the challenges of managing PCOS can lead to significant psychological distress, including anxiety, depression, and body image issues, highlighting the need for psychological support and counseling [17]. This extensive range of symptoms necessitates a holistic and multidisciplinary approach to managing PCOS, focusing on personalized interventions that address the reproductive, metabolic, and psychological needs of affected individuals to improve their quality of life and long-term health outcomes, incorporating lifestyle modifications, pharmacological interventions, and psychological support.

4. Diagnosis

The diagnosis of PCOS presents a substantial clinical challenge, primarily due to the syndrome's broad spectrum of clinical manifestations, which exhibit considerable inter-individual variability and overlap with other endocrine disorders, leading to a significant number of undiagnosed cases and delayed interventions, thereby impacting patient outcomes and potentially exacerbating long-term health risks [18]. This diagnostic complexity is further compounded by the absence of a singular, definitive diagnostic test, necessitating a comprehensive evaluation that integrates clinical, biochemical, and imaging findings to establish an accurate diagnosis, and requires a high degree of clinical acumen and awareness of the nuanced presentations of PCOS. This complexity often necessitates a multifaceted approach, involving detailed patient history taking and careful physical exam.

Genetic factors are strongly implicated in the development of PCOS, underscoring a significant hereditary component and highlighting the crucial role of familial predisposition in the syndrome's etiology, and necessitating a thorough exploration of family history during the diagnostic process [2]. Research suggests that PCOS arises from the intricate interaction of multiple genes, rather than a single genetic

mutation, reflecting the polygenic nature of PCOS and the complexity of its inheritance patterns, which involves complex gene-environment interactions [19]. Modern genetic research, through large scale genome-wide association studies, has pointed toward specific genes of increased involvement, however more research needs to be completed.

Beyond genetic influences, environmental factors, encompassing dietary habits, physical activity levels, and exposure to endocrine-disrupting chemicals, play a pivotal role in modulating the expression and severity of PCOS, contributing to the variability in clinical presentation, and highlighting the importance of assessing lifestyle and environmental exposures in patient evaluations. These environmental exposures can create epigenetic changes, and these changes can cause the upregulation of the genes that contribute to the symptoms of PCOS.

The diverse clinical presentations of PCOS often lead patients to seek care from a variety of healthcare providers, including internists, family practitioners, gynecologists, and endocrinologists, resulting in a fragmented care pathway that can further complicate and delay the diagnostic process, as each provider may approach the condition with a different focus or management strategy, underscoring the need for improved communication and coordination among healthcare professionals, perhaps utilizing team based approaches in healthcare. To ensure accurate diagnosis and effective management of PCOS, a thorough understanding of its complex causes and diverse clinical implications is essential, requiring a multidisciplinary approach that integrates the expertise of various healthcare professionals, including endocrinologists, reproductive endocrinologists, dermatologists, psychologists, and nutritionists.

The diagnosis of PCOS is primarily based on the Rotterdam criteria, which mandate the presence of at least two of the following three criteria: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound (after excluding other potential causes) [20]. It is imperative to meticulously exclude other conditions that can mimic PCOS, such as thyroid disorders, hyperprolactinemia, and non-classical congenital adrenal hyperplasia, to prevent misdiagnosis and ensure appropriate management, which requires a systematic and thorough differential diagnosis [21]. This meticulous and comprehensive evaluation, encompassing a detailed medical history, physical examination, hormonal assessments, and imaging studies, is paramount to accurately diagnose PCOS and initiate appropriate management strategies, ultimately improving patient outcomes and quality of life and reducing the long-term health risks associated with untreated PCOS. This process should include a thorough patient interview, examining menstrual history, hirsutism, acne, and weight fluctuations, and a comprehensive physical exam to evaluate for signs of hyperandrogenism and insulin resistance. The hormonal assessments should include testing for testosterone, LH, FSH, estradiol, and potentially other androgens, while the ultrasound should be performed by a radiologist with expertise in gynecological imaging in order to clearly evaluate the ovarian morphology. Additionally, due to the mental health comorbidity of PCOS, patient evaluation should include screening for depression and anxiety.

5. Treatment

PCOS is a multifaceted endocrine disorder affecting women of reproductive age, necessitating a nuanced and highly individualized management approach due to its diverse symptom presentation, which includes irregular menstrual cycles, excess

androgen production, and polycystic ovaries [22, 23]. This complexity demands a comprehensive understanding of the intricate interplay between hormonal imbalances and their systemic effects, recognizing that PCOS extends beyond mere reproductive dysfunction, significantly impacting metabolic, dermatological, and psychological health and requiring a holistic approach that acknowledges the interconnectedness of these domains. Addressing hormonal imbalances is paramount and typically involves pharmacological interventions such as oral contraceptives to regulate menstrual cycles and reduce androgen levels, thereby mitigating symptoms such as hirsutism, acne, and menstrual irregularities and improving long-term reproductive health while also considering the benefits for bone health and potential mood stabilization, and the impact on quality of life [1]. Concurrently, insulin-sensitizing agents like metformin are employed to mitigate insulin resistance, a key factor in PCOS pathophysiology, and to reduce the risk of associated metabolic complications such as type 2 diabetes, cardiovascular disease, and nonalcoholic fatty liver disease, thereby addressing the systemic ramifications of PCOS and preventing long-term morbidity [24].

Concurrently, lifestyle modifications, encompassing increased physical activity and a balanced diet, are crucial components of management, contributing to weight loss and offering significant health benefits, particularly in improving insulin sensitivity, reducing hyperandrogenism, and addressing the psychological impact of weight-related symptoms and enhancing overall quality of life [25]. These modifications should be tailored to individual patient needs and preferences, incorporating strategies for sustainable behavior change, such as cognitive behavioral therapy, motivational interviewing, and nutritional counseling, to support long-term adherence and empower patients to actively participate in their care. Given PCOS's association with an increased risk of metabolic, endocrine, and cardiovascular complications, a comprehensive management strategy is essential, including regular monitoring and proactive screening for comorbidities to prevent long-term health sequelae, and to address the potential for increased risk of endometrial cancer due to chronic anovulation, as well as the risk for depression, anxiety, and sleep disorders, and to promote preventive health measures [24].

Proper diagnosis and management are indispensable to address patient concerns and prevent complications, with current understanding emphasizing the importance of understanding symptoms from the patient's perspective, as the impact of symptoms varies significantly among individuals, and recognizing the significant burden PCOS places on quality of life [23]. This patient-centered approach recognizes the subjective experience of PCOS and the need for individualized care, acknowledging that PCOS affects each patient's life differently, and emphasizing shared decision-making and patient empowerment. PCOS management is thus highly individualized, focusing on specific symptoms and concerns, and encompasses a range of treatment strategies, including: lifestyle modifications, wherein weight loss, regular exercise, and a healthy diet are crucial for improving insulin sensitivity and reducing hyperandrogenism, and addressing the psychosocial implications of the condition through mental health support, counseling, and peer support groups [25]; pharmacological interventions, involving oral contraceptives to regulate menstrual cycles and manage hirsutism and acne, and to provide contraception when desired, while also understanding contraindications and risks, and monitoring for potential side effects [26], metformin to improve insulin sensitivity and manage insulin resistance and metabolic complications, and to potentially improve fertility outcomes, while monitoring for potential side effects and adjusting dosage based on patient response

[27], antiandrogens to treat hirsutism and acne, and to address the emotional distress associated with these symptoms, while considering long-term safety and potential drug interactions [28], and ovulation induction agents like clomiphene citrate or letrozole for women desiring pregnancy, and to improve the chances of conception, alongside monitoring and fertility specialist care, and considering the risks of multiple gestations [29]; and assisted reproductive technologies (ART), which may be considered for women with PCOS who are unable to conceive with other treatments, and to provide a pathway to parenthood for those with severe infertility, incorporating the ethical and financial implications, and providing comprehensive counseling [30]. This multifaceted approach underscores the need for a personalized and integrated treatment plan to effectively manage PCOS and improve the overall well-being of affected women, encompassing medical, psychological, and social support, and fostering a collaborative relationship between patient and healthcare provider, and emphasizing patient education and self-management.

6. Conclusion

PCOS presents a significant and multifaceted challenge to women's health, impacting reproductive, metabolic, and psychological well-being. Its complex etiology, involving genetic predispositions and environmental factors, results in a heterogeneous clinical presentation, making diagnosis and management intricate. The Rotterdam criteria provide a standardized approach to diagnosis, emphasizing the importance of excluding other potential causes.

Effective management of PCOS necessitates a personalized approach, addressing individual symptoms and concerns. Lifestyle modifications, including weight management and exercise, are foundational, while pharmacological interventions, such as oral contraceptives, metformin, and antiandrogens, target specific hormonal imbalances and metabolic dysfunctions. For women with fertility concerns, ovulation induction agents and assisted reproductive technologies offer viable options.

Ongoing research continues to elucidate the underlying pathophysiology of PCOS, aiming to improve diagnostic accuracy and develop more targeted therapies. A comprehensive understanding of the syndrome's diverse manifestations and a multidisciplinary approach to care are crucial for optimizing outcomes and enhancing the quality of life for women affected by PCOS.

Conflict of interest

The authors declare no conflict of interest.

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Section 2

The Symptoms of Polycystic Ovary Syndrome

Chapter 2

Unmasking the Overlooked Symptoms of PCOS: Navigating Ovulatory Dysfunction, Menstrual Disorders, and Acne

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Abstract

Polycystic ovarian syndrome (PCOS) is a prevalent multifactorial endocrine disorder primarily affecting women of reproductive age, though it may present across a broader age spectrum. Diagnosis in adults requires meeting at least two of the following three Rotterdam criteria: ovulatory dysfunction, clinical or biochemical evidence of hyperandrogenism, and polycystic ovarian morphology on ultrasonography or elevated anti-Müllerian Hormone (AMH) levels. Clinical manifestations often include menstrual irregularities, subfertility, and dermatological features such as acne, hirsutism, frontal alopecia, and acanthosis nigricans. Ovulatory dysfunction is the most common cause of infertility in PCOS, contributing to approximately 90% of cases. Additionally, prolonged anovulation may increase the risk of endometrial hyperplasia and, in some instances, endometrial carcinoma. A comprehensive clinical evaluation should assess menstrual history, body mass index (BMI), and dermatological signs of hyperandrogenism. Management is individualized, based on symptom severity and reproductive goals. Lifestyle modification and weight reduction are foundational interventions, particularly for overweight or obese patients. For those seeking conception, first-line pharmacological treatments include ovulation induction agents such as clomiphene citrate and letrozole. Metformin is frequently employed to address insulin resistance and impaired glucose tolerance. For women not pursuing pregnancy, combined hormonal contraceptives are the preferred treatment for menstrual regulation and amelioration of androgenic symptoms. Long-term management of PCOS necessitates a holistic approach that integrates metabolic, reproductive, and dermatologic considerations, with the aim of improving both clinical outcomes and quality of life.

Keywords: menstrual disorder, ovulatory dysfunction, acne, hyperandrogenism, ovulation induction

1. Introduction

PCOS stands out as the most common metabolic syndrome, prevalent among females during their reproductive lifespan, often starting in adolescence and continuing into later stages of life, including after menopause. It affects around *10%* of women globally [1].

Currently, the diagnostic standard that gained broad clinical acceptance for PCOS is the *Rotterdam criteria*, set up in 2003 through a collaboration between the ESHRE and the ASRM [2]. As per these guidelines, establishing the diagnosis mandates *no less than two of the below-mentioned three* parameters:

i. Oligo or anovulation

ii. Abnormally elevated androgens, confirmed through observable clinical findings or lab tests

iii. Polycystic ovarian appearance on ultrasound, defined by the volume of either ovary not less than 10 mL, or at least 20 Follicle count in total, or 10 follicles in a cross-section, in any of the ovaries.

In clinical settings, PCOS patients commonly report *menstrual disturbances*, *difficulty conceiving*, and symptoms related to *increased androgen activity* [3]. Menstrual symptoms may include scanty periods, heavy bleeding, skipped cycles, or prolonged absence of menstruation (amenorrhea) [4]. Other physical signs of dysregulated androgens include acne, excessive hair growth, and scalp hair thinning. Effectively managing these issues requires a solid grasp of the hormonal mechanisms driving PCOS and how they manifest physically.

2. The hormonal symphony: The functional dynamics of the HPO axis

The key aspects of a woman's reproductive health are significantly shaped by a properly functioning HPO axis, a coordinated system for the release of the vital hormones responsible for triggering and sustaining ovulation, the GNRH, the gonadotropins, and the ovarian hormones. The reproductive cycle is regulated by the arcuate nucleus, a specialized hypothalamic region, where the coordinated pulses of GnRH are released at intervals periodically. This hormone, via the hypothalamo-pituitary portal stream, reaches adenohypophysis, stimulating it to secrete FSH and LH. FSH drives folliculogenesis, which then begins producing the hormone estradiol. With continued follicular development, estradiol levels gradually increase and eventually surpass a specific threshold, initiating feed-forward signaling on the pituitary and the hypothalamus. This is responsible for the immediate and steep rise in LH concentration, the main hormonal stimulus for ovulation. The Corpus luteum, the transformed follicle post-ovulation, begins to secrete an increasing amount of progesterone. Progesterone, in conjunction with estradiol and inhibin B, sends back the inhibitory signals, resulting in diminished FSH, LH, and GnRH. This negative feedback mechanism helps maintain hormone balance and ensures the menstrual cycle pattern [5, 6].

3. Tracing the hormonal dysfunction: The neuro ovarian crosstalk

Disturbances in the HPO axis can cause irregular hormonal milieu in the form of altered GnRH rhythm, LH/FSH disproportion, and escalated ovarian and adrenal production of androgens [7]. A raised LH concentration is observed in nearly 75% of the PCOS population, and an abnormal LH/FSH ratio in around 94%. This LH stimulus to the ovarian stromal and thecal cells generates more androgens, which interfere with normal follicular development and hinder follicular selection. Despite this, the small antral follicles continue to produce estradiol in amounts typical of the early follicular phase. Concurrently, the androgen-androstenedione enhances the amount of estrone in the body by its peripheral conversion. The combined elevation of estradiol and estrone intensifies LH secretion by amplifying both its pulse frequency and amplitude, thereby maintaining the cycle of anovulation [8]. Simultaneously, increased estrogen levels suppress FSH secretion, hindering follicular development. This creates a negative feedback loop of high androgens and low FSH, preventing the dominant follicular maturation and sustaining anovulation. Over time, this cycle contributes to the formation of polycystic ovaries. While the altered LH/FSH ratio has no diagnostic role any longer, it is still used as a supportive test for diagnosis in select geographical areas, including China and Japan [9, 10].

AMH plays an indispensable role in regulating the GnRH neuronal activity. Studies show that the interaction of AMH with its respective receptor targets on the GnRH-secretory neurons may influence the frequency and magnitude of the GnRH pulses [11]. In PCOS, elevated AMH levels may activate hypothalamic pathways, contributing to excessive androgen production. AMH also inhibits the development of follicles destined for ovulation, particularly affecting the granulosa cells [12]. Research in murine models suggests that follicles are more sensitive to FSH in an AMH-free environment, indicating that follicular development is hindered due to AMH by diminishing the FSH responsiveness and downregulating the aromatase in granulosa cells [13].

3.1 Implications of ovulatory dysfunction in PCOS

In PCOS, anovulation is often linked to the premature cessation of antral follicular growth before achieving the preovulatory maturity stage. Ovaries affected by PCOS typically appear enlarged and contain numerous small follicles along the outer edge, forming a "string of pearls" pattern visible on ultrasound. These ovaries also show increased stromal echogenicity and blood flow.

Ovulatory dysfunction in PCOS often leads to symptoms such as amenorrhea, abnormal uterine bleeding, and infertility [14, 15]. Oxidative stress has been identified as a factor that disrupts normal follicular development and maturation [16–18]. Additionally, it is observed that the levels of ovarian follicular fluid neurotensin (NTS), a neuropeptide that has a role in governing the ovulatory process, have been significantly reduced in PCOS, although its exact role in the disorder remains unclear [19].

3.2 Menstrual irregularities

Most women with PCOS experience *disrupted menstrual cycles*, typically starting soon after their first period, without ever developing consistent monthly cycles.

About *75–85%* of individuals with PCOS will show some form of menstrual irregularity. These issues stem from a lack of regular ovulation, causing inconsistent estrogen effects on the uterine lining.

Managing menstrual disturbances in women with PCOS requires insight into the hormonal imbalances that hinder ovulation. One of the key factors is an accelerated GnRH output from the hypothalamus, subsequently triggering a heightened pituitary LH secretion relative to FSH, disrupting the physiological follicular maturation and ovulation. As a result, the follicles are locked in an early developmental phase, preventing full growth and rupture. Due to the anovulation, the progesterone feedback, which normally helps regulate LH secretion, becomes unavailable, thus leading to a persistently elevated LH level. Meanwhile, FSH levels remain low to normal, suppressed by high levels of *estrone*—converted from excess androgens in body fat, and *inhibin B*, produced by numerous small ovarian follicles. These hormonal imbalances often result in a disproportionate rise in LH in comparison to FSH, with a ratio often ranging from *2:1 to 3:1*. This hormonal environment causes irregular or absent menstrual bleeding, due to unpredictable endometrial development and shedding under unbalanced estrogen stimulation.

One major concern in long-standing PCOS is the risk posed by *continuous estrogen exposure* in the *absence of progesterone*, which is normally produced following ovulation. This hormonal imbalance encourages excessive growth of the uterine lining (endometrium), potentially progressing to *atypical hyperplasia* or even *endometrial cancer* over time. Around *85% of endometrial cancers* are linked to estrogen and tend to be well-differentiated, making *PCOS a significant risk factor* for this type of malignancy [20–22].

Obesity is a frequent finding, affecting around *40–60%* of PCOS patients [23]. Excess weight contributes to *elevated androgen levels* by lowering *SHBG,* which elevates the active testosterone levels in the bloodstream. Obesity further exacerbates ovulatory dysfunction, making menstrual problems more persistent.

3.3 Weight management, and building sustainable habits: A key to metabolic regulation

Lifestyle intervention, especially weight reduction, is widely recognized as the primary approach for PCOS [24]. The primary goals are reduction of body weight and maintaining weight control while avoiding the likelihood of regaining it. The *Endocrine Society* recommends *weight control* as a foundational step in treating PCOS-related menstrual disturbances, particularly in the obese. Efforts should concentrate on *reducing calorie intake*, though no specific dietary plan has been proven universally superior [25]. The emphasis is placed on choosing a diet that is *nutritionally sound, safe, and sustainable* over the long term.

3.4 Balancing life: Balancing hormones

Lifestyle modification strategies that combine healthy *eating habits*, *regular exercise*, *behavioral therapy*, and *stress management* are the most effective. Adding moderate physical activity—such as 30 minutes a day of walking or other aerobic exercise, can help improve hormonal imbalance and metabolism in PCOS [24]. Existing evidence is grounded on observational study designs rather than randomized trials. A consistent finding is that even a modest *5–10% reduction in weight can support improved ovulation* and *more regular menstrual cycles.*

4. Advanced interventions in weight management

4.1 Pharmacotherapy

In cases where lifestyle interventions are insufficient, *medical therapy for weight loss* or even *bariatric surgery* may be considered. Orlistat, a lipase inhibitor—functions by inhibiting gastric and pancreatic lipases, thereby reducing the digestion and absorption of dietary fats. Sibutramine is an SNRI, acting centrally, enhancing satiety and energy expenditure. Rimonabant, an antagonist of the cannabinoid receptor type 1 (CB1), is known to suppress appetite and aid in controlling lipid metabolism, glucose homeostasis, and adipose tissue activity [26–29].

Evidence from studies in the general obese population suggests these agents not only result in greater weight loss but also sustain healthy body weight and metabolic optimization compared to lifestyle interventions alone. Nevertheless, pharmacotherapy must be administered under close medical supervision due to potential side effects and weight regain, which is frequently observed after discontinuation. The specific effects of these medications on metabolic and endocrine parameters in obese women with PCOS remain inadequately understood and necessitate more robust evidence to evaluate the safety and efficacy of this subgroup. The World Health Organization advocates for the inclusion of pharmacological agents as part of a broader weight management strategy that includes dietary restriction and lifestyle modification.

4.2 Role of surgery

For individuals suffering from severe obesity, bariatric surgery is often advised as the most intensive form of weight-reducing measure, typically for morbid obesity, or class-2 obesity with a coexistent obesity-related health condition. Bariatric surgery has been shown to promote a notable reduction in weight, alongside the peripheral *insulin refractoriness*, and the risk of associated *metabolic disorder complex*. It can help resolve *hyperandrogenism* and its symptoms, leading to the resumption of the physiological patterns of menstruation and increasing fertility among those who had trouble conceiving [30].

Although the positive influence of weight reduction on health is widely recognized in obese individuals, the potential for weight loss to restore ovulatory function in the PCOS population with average BMI is yet to be thoroughly studied. To summarize, the metabolic effects of weight management vary among women with PCOS, and not all will experience the return of ovulation.

4.3 Cycle control and beyond: The power of hormonal preparations

For those not actively pursuing pregnancy, *combined hormonal contraceptives (CHCs)* are typically used as the primary treatment to manage menstrual irregularities. An important benefit of CHC use in PCOS is the effect of progesterone counteracting the prolonged estrogen exposure, which is accountable for its ability to *lower the occurrence of premalignant and malignant endometrial lesions. Progestin-only options*, including cyclic oral tablets, hormone-releasing implants, and intrauterine systems, can also help reduce this risk.

CHCs function by reducing the release of *GnRH* and *pituitary hormones* such as *LH*, which are often elevated in PCOS. This hormonal suppression contributes to lower ovarian *androgens* and *estrogens*. In addition, *ethinyl estradiol*, a component

of CHCs, increases the hepatic SHBG synthesis, thus lowering the circulating free androgens [31]. The *progestin* component of CHCs also helps by blocking *5α-reductase*, which limits the metabolism of testosterone to a stronger active metabolite. Some may interfere with *androgen receptors*, enhancing their anti-androgenic effects [32, 33]. However, despite numerous studies evaluating their contribution to improving hormonal patterns and symptoms like hirsutism in PCOS, *no specific formulation is established to have more efficacy* in improving cycle regulation [34].

Data so far do not convincingly support that CHCs are more effective than non-oral options, such as patches or vaginal rings, in treating symptoms of polycystic ovary syndrome (PCOS). Therefore, the patient's autonomy should guide the mode of hormonal delivery. Continuous administration of CHCs, without hormone-free intervals, has been shown to provide more consistent suppression of ovarian activity compared to cyclic use, by preventing the temporary ovarian function rebound that can occur during hormone breaks.

It is important to inform patients that *irregular or unexpected bleeding* is a common issue with progestin-only methods, with a significant portion of users—up to 89%—experiencing some form of an altered bleeding pattern, even though the *protective effect on the endometrium* remains intact [34].

4.4 Tackling insulin resistance (IR)

A solid relationship exists between insulin resistance and menstrual irregularities. Research shows that those who experience irregular cycles often have reduced insulin sensitivity compared to those with regular menstruation. The length and pattern of the menstrual cycle may therefore serve as an indicator of underlying insulin resistance [35]. This association is consistent with findings that the PCOS population with a coexistent IR is likely to demonstrate lesser ovulation rates. As a result, medications that improve insulin sensitivity have been evaluated for their potential to support ovulatory function in these patients.

Metformin, a biguanide medication primarily used to manage blood glucose levels, has been widely investigated for its role in improving ovulation in PCOS. It reduces blood sugar and insulin levels by inhibiting hepatic glucose production and countering glucagon activity [36]. Metformin appears to lower excessive hormone levels and support the regulation of follicular growth in the ovary, although the precise mechanism behind these effects is still unclear. Nonetheless, experts recommend its use as a second-line therapy, to help restore menstrual cycles in women who are unable to take combined hormonal contraceptives (CHCs), or attempting pregnancy, or when lifestyle modifications alone are insufficient. Observational studies have also shown that long-term metformin treatment can help normalize menstrual cycles, with reported benefits extending for up to a decade.

In *2017, a Cochrane review* of PCOS females concluded that improved ovulation (OR 2.55) and menstrual frequency (OR 1.72) were observed with metformin relative to no intervention [37]. Additionally, a retrospective study following patients for 10 years reported improvements in cycle regularity within the first year of treatment, with many participants achieving normalized menstruation. The study used a total metformin dose of 2 g a day in overweight PCOS individuals with normal initial glucose levels. Only a small number (3%) discontinued treatment in the initial year, given adverse effects, which were generally mild and temporary—mainly nausea and diarrhea [38].

While metformin offers some benefits for menstrual regulation, for women who are not keen on conception, *CHCs remain more effective* and are considered the

preferred option. Although metformin also supports weight loss and improves lipid profiles, combining it with CHC does not appear to provide additional advantages in regulating the menstrual cycle [39].

In conclusion, *irregular or absent ovulation* is a primary characteristic of PCOS and often results in menstrual disturbances. For a population with a higher BMI, the recommended initial management is behavioral modification. For individuals not intending to become pregnant, CHCs are a good option to regularize the cycles, with a subsequent protective benefit against endometrial hyperplasia and cancer. Metformin is a viable alternative for those who are trying to conceive or for whom hormonal contraceptives are unsuitable. Healthcare professionals should ensure patients understand the potential health implications of persistent anovulation and provide treatment recommendations based on each person's medical condition and reproductive intentions [38].

4.5 Infertility in PCOS and the path to parenthood

PCOS is a principal contributor to female infertility related to anovulation, yet the mechanism behind the inconsistent or diminished ovulation is only partially understood. Adopting behavioral health strategies including a regulated diet plan, and consistent physical activity are proven strategies to help manage insulin resistance hyperandrogenism, hormonal imbalance, dyslipidemia, and cardiovascular health. However, the direct impact of lifestyle changes *on fertility remains inconclusive.* Some research suggests that achieving a healthy weight in those who are obese helps in the resumption of ovulation, thereby enhancing the effectiveness of ovulation induction treatments, and potentially improving conception and successful delivery outcomes [40]. Nevertheless, lifestyle changes should serve as the primary intervention regardless of fertility goals. Weight management supports the normalization of ovulation, thus regulating the menstrual cycles. A study that enrolled more than 5000 participants found that physical activity, regardless of the type, positively impacts fertility in obese women [41]. Additionally, a meta-analysis encompassing 13 trials concluded that the clinical endpoints, including regularization of menstruation and conception rates, do not significantly differ when comparing lifestyle interventions with metformin. Notably, the combination of metformin with lifestyle changes did not significantly improve BMI reduction. Despite this, weight loss remains a highly effective and accessible approach with minimal side effects, making it a preferred frontline therapy for managing infertile females who are overweight [42]. Subfertility management in PCOS often combines lifestyle changes, pharmacological therapies, surgical options, and assisted reproductive technologies (ART).

5. Harnessing the ovulation induction with oral ovulogens

5.1 Clomiphene citrate (CC)

It is commonly utilized as one of the primary treatments to stimulate ovulation in anovulatory PCOS. As a SERM, it has variable actions on estrogen receptors at different sites. At the hypothalamus, the receptors are blocked by the CC, disrupting the normal estrogen feedback mechanism. This leads to an increased pulsatility of GnRH secretion, prompting more FSH release by the adenohypophysis, which encourages follicular growth and maturation. Studies have demonstrated that CC improves ovulation rates and pregnancy outcomes more effectively than placebo [43]. Clomiphene citrate is usually prescribed in a daily dosage varying

between 50 and 150 mg over 5 days, typically beginning between the 3rd and 5th day of the period. The dose of further cycles may be sequentially increased by 50 mg in case of absent ovulation [44]. According to Homburg's recommendations, an initial CC dose of 100 mg/day, commencing from the 4th or 5th day of periods, is advisable since increasing the dose beyond this level does not yield further benefits. Clinical data indicate that after 6 months of CC therapy, over 70% of women achieve ovulation, with 36% becoming pregnant and 29% ultimately delivering a live birth. Resistance to clomiphene citrate may be affected by several factors, including a higher BMI, advanced age, androgen excess, diminished insulin sensitivity, etc. Clomiphene-induced estrogen receptor downregulation may lead to suboptimal endometrial development and diminished cervical mucus quality, both of which can adversely affect fertility outcomes.

5.2 Letrozole

It lowers estrogen levels via the enzymatic blockage of aromatase, the enzyme responsible for converting androgens into estrogens in the ovaries and other tissues. This reduction in estrogen promotes folliculogenesis by augmenting the GnRH pulses and FSH secretion and releasing feedback suppression on the higher centers. Compared to clomiphene citrate, letrozole tends to cause fewer occurrences of multiple follicle development, reducing the incidence of multifetal gestation and OHSS [45, 46]. Unlike clomiphene citrate, which may lead to the depletion of estrogen receptors and consequently impair endometrial thickness or cervical mucus quality, letrozole exerts minimal anti-estrogenic effects on these reproductive parameters, potentially enhancing endometrial receptivity. Due to its favorable pharmacological safety profile, letrozole is a preferential agent of choice for females undergoing ovulation induction, including clomiphene-resistant PCOS, and those with anovulatory cycles or unexplained infertility [47, 48].

5.3 Gonadotropins

If ovulation induction with first-line agents is unsuccessful, gonadotropins are typically introduced as a second-line treatment. Often, due to the disproportionate high LH over FSH, administration of exogenous FSH is considered more physiologically appropriate in PCOS. However, gonadotropin therapy can lead to the development of multiple follicles, often predisposing women to OHSS or pregnancies of higher order. The likelihood of such risks is minimized by choosing a gradual dose escalation regime, usually combined with careful ultrasound monitoring to track follicular response [48]. If more than three follicles exceed 14 mm in diameter, it is recommended to withhold the ovulation trigger and consider cycle cancelation to prevent adverse outcomes. In the context of excessive ovarian response, the use of hCG should preferably be avoided due to its potential to exacerbate ovarian hyperstimulation. Patients should be informed about the associated risks. OHSS may develop typically with the overstimulated multiple follicles, presenting with any of the following symptoms: nausea, vomiting, abdominal bloating, pelvic pain, and, in more severe cases, respiratory compromise [49].

5.4 LOD: An operative alternative for overcoming ovarian resistance

For targeting the resistant Ovulatory dysfunction to induction by the routinely used ovulogens, LOD may be an alternative to gonadotropin therapy. LOD works by

using electrocoagulation to perforate the ovaries, curtailing the ovarian androgens and improving the function of the HPO axis. This procedure induces ovulation of a single follicle, thus avoiding the complications linked with multiple follicular development [50]. LOD is particularly beneficial for women with CC resistance and elevated LH levels. It may be appropriate in patients already undergoing laparoscopic evaluation, or whenever rigorous monitoring associated with gonadotropin protocols is not feasible. LOD is minimally invasive and aims to limit ovarian damage while promoting ovulation. Studies indicate a 34% cumulative pregnancy rate with LOD, compared to 67% with FSH treatment [50]. For women who fail to ovulate after LOD, CC is often prescribed, and if ovulation remains absent, FSH may be introduced.

5.5 Hope through technology: ART in PCOS

When conventional therapies are unsuccessful, assisted reproductive technologies (ART) serve as third-line interventions. ART encompasses a range of methods, including IUI, IVF, IVM, and ICSI. IUI may be considered for individuals who achieve ovulation through induction but face additional infertility challenges, such as cervical or male factor infertility. IVF is indicated when conception does not occur following ovulation induction, particularly in the presence of coexisting factors like tubal pathology or significant male subfertility. IVF treatment in a PCOS female places her at a higher risk for OHSS, necessitating vigilant monitoring and individualized treatment planning. Additionally, these patients may experience a higher miscarriage rate compared to their non-PCOS counterparts. ART protocols employing GnRH agonists have proven effective in modulating luteinizing hormone (LH) levels, promoting follicular growth while minimizing the risk of excessive LH secretion. This strategy has shown promise in reducing OHSS incidence and enhancing reproductive outcomes in women with PCOS [51–53].

5.6 Cutaneous clues: Acne as a marker of PCOS

The possible hyperandrogenic dermatological manifestations of PCOS include acne, hirsutism, androgenic alopecia (female pattern hair loss), acanthosis nigricans, etc. [54]. Acne vulgaris is a long-term, mild inflammatory skin condition that predominantly affects adolescents and adults. It is often a visible sign of the underlying hormonal imbalance seen in PCOS [55]. The condition primarily impacts the pilosebaceous unit, a key component in maintaining skin health and regulating sebum production, leading to the development of acne.

6. Hormonal and inflammatory cascade: The basis of acne in PCOS

The underlying pathophysiology is interlinked among a combination of four key factors [56]:

1. Augmented sebum production with altered composition;
2. Proliferation of C. acnes and other virulent skin flora;
3. Dysregulated keratinocyte turnover and obstruction of the pilosebaceous unit;
4. Inflammation and immune response.

The occurrence of acne in PCOS can be attributed to hormonal disturbances, notably elevated androgen levels, insulin resistance, and inflammatory activity. Primarily, it affects the areas with maximal sebaceous gland concentration, namely the facial skin and the upper torso, often extending to the arms. Papules, pustules, and nodules are the inflammatory manifestations—while non-inflammatory acne includes comedones, otherwise termed the black and the white heads.

Under normal conditions, the sebum produced in sebocytes has a barrier role due to its antioxidant and antimicrobial activity. Androgen receptors are located at different parts of the pilosebaceous unit in variable concentrations. 5α-reductase metabolizes the androgen-testosterone to dihydrotestosterone and thus promotes an exaggerated local androgen interaction with the receptors in the hair-sebaceous gland complex. This interaction enhances sebum production with excess lipid contents that can be directly correlated with the severity of acne [57].

Additionally, the Epidermal growth factor, Keratinocyte growth factor, Insulin-like growth factor 1, etc. also modify the sebum. Insulin regulates the steroid hormone levels by multiple mechanisms. It directly stimulates the androgen generation by ovarian theca cells and further potentiates the LH-driven activation of theca interna. It regulates the biosynthesis and metabolism of peripheral androgens. Diminishing SHBG production by the liver elevates the unbound testosterone levels. It increases the levels of circulating free testosterone by reducing the synthesis of SHBG by the liver [58]. The disordered keratinocyte turnover with accelerated cell division and abnormal shedding, together with the surplus sebum, causes the clogging of the follicular unit, inducing microcomedogenesis, which later transforms into noticeable acne lesions [59].

Cutibacterium acnes, a gram-positive anaerobic diphtheroid, is a part of the skin microbiome. It breaks down the triglycerides in the lipid-enriched sebum to glycerol and fatty acids, thus setting up a predominant low-oxygen milieu and promoting the preferential colonization of pathogenic flora. The host inflammatory signaling in response to C. acnes liberates various cytokines that recruit the immune cells and generate free Oxygen radicals. As the inflammation progresses, the follicle finally ruptures, releasing its contents into the dermis and causing inflammatory acne.

6.1 Clinical profile and diagnostic evaluation

An accurate diagnosis of acne in PCOS involves examining its type and severity. Acne can be divided into comedonal or inflammatory types. The Global Acne Grading Scale (GAGS) grades acne into no acne, mild, moderate, or severe [60]. The Burke and Cunliffe counting method is another multimodal imaging technique used for evaluating acne. Additional signs of elevated androgens, such as hirsutism, should be investigated. Ferriman Gallwey's scoring indicates the severity of hirsutism and, indirectly, the quantity of androgens. BMI and waist-hip ratio are to be documented.

Biochemical documentation requires measuring total testosterone, free testosterone, and DHEA-S. Free testosterone provides a more accurate diagnostic result, and the quantification of free testosterone can be performed using techniques such as equilibrium dialysis or ultracentrifugation. Alternatively, free testosterone levels can be estimated using the Vermeulen equation, which relates total testosterone and SHBG levels. Additional investigations may be required to distinguish from alternative possibilities, including non-classical CAH or Cushing's.

6.2 Concerns beyond cosmesis

The compromised facial esthetics trigger social awkwardness, low self-esteem, and emotional distress. Patients suffer from the psychological problems associated with dermatological scarring, a result of the long-term inflammation.

6.3 Integrated management strategies

The management of acne related to PCOS involves addressing both the symptoms and the underlying causes. A multifaceted treatment approach is necessary to improve skin condition and balance the hormonal and metabolic abnormalities. Prompt treatment can restore hormonal equilibrium and enhance insulin sensitivity, which not only improves acne but also helps manage other PCOS symptoms.

Treatment Goals:

- Reduce inflammation
- Regulate keratinocyte turnover
- Limit *C. acnes* colonization
- Decrease sebum production by controlling androgen levels

a. *Lifestyle Modifications*

Lifestyle interventions are multi-component, including physical activity, diet, weight management, and behavioral strategies. It improves the metabolic parameters, thereby correcting the PCOS-related pathophysiology.

b. *Diet*

A low GI diet helps mitigate insulin resistance, thus helping curb the acne lesions.

c. *Patient Education*

Patients should be informed that acne treatment may take several weeks to show results. Typically, facial acne improves within 4–6 weeks, with an additional 3–4 weeks required for noticeable improvement in other affected areas, such as the chest and back.

d. *Topical and Systemic Acne Treatments*

Benzoyl Peroxide: This topical agent works by generating reactive oxygen species that have bactericidal, anti-inflammatory, and comedolytic effects.
Antibiotics: Due to increasing resistance, antimicrobials are typically used in combination with other treatments like benzoyl peroxide to target the inflammatory aspects of acne.
Retinoids: Retinoids, such as isotretinoin, adapalene, and tazarotene, are effective for treating comedonal acne. They help normalize skin cell turnover. Therapy starts with lower-potency retinoids, which are gradually increased to minimize

irritation. Isotretinoin is commonly prescribed, yet retinoids are advised cautiously in the reproductive age group given their teratogenicity.

e. *Hormonal Treatments*:

Combined Estrogen-Progestin Pills: Owing to their capacity to lower sebum production by suppressing androgen activity, OCPs are harnessed as one of the frontline medications to tackle the acne in PCOS. Monophasic OCPs containing ethinyl estradiol (≥20 mcg) and progestin are often used either as monotherapy or in conjunction with alternate anti-acne medications. In certain cases, acne may worsen due to the progesterone component; in such cases, a progestin with anti-androgenic properties or reducing the estrogen dose may help mitigate this effect.
Anti-androgens: Anti-androgens act by decreasing sebum production. Though the FDA does not endorse their use due to potential harmful effects, they are seldom used in intractable hyperandrogenic acne. Spironolactone, an aldosterone antagonist, is often used alongside contraceptives due to its potential teratogenic effects. Other anti-androgens, such as finasteride and dutasteride, may be considered, but they come with potential risks, including hepatotoxicity and teratogenicity. Women taking these medications must avoid pregnancy and use contraception during treatment [61].

f. Insulin Sensitizers:

Metformin: To decrease insulin resistance, Metformin can be added at a dose of 1–2 grams BD.

7. Conclusion

On average, 90% of infertility cases can be attributed to PCOS-related ovulation abnormalities. Tailoring treatment to the individual case-specific clinical context is critical for achieving optimal outcomes. In obese women, strategies focusing on dietary regulations and physical activity are the primary recommended strategies, as such strategies may positively influence overall metabolic and reproductive health. For patients who are unable to implement lifestyle changes, pharmacological treatments or surgeries addressing obesity can be utilized as alternative approaches.

Therapies that aid in stimulating ovulation generally yield favorable cumulative pregnancy rates with a low incidence of multiple gestations, although careful monitoring of follicular development remains essential. Multiple options exist for promoting ovulation in these individuals. While the age-old drug Clomiphene has been serving as one of the primary options, emerging evidence supports letrozole as a superior alternative. Metformin demonstrates some benefits, but its impact on live birth rates is modest. When initial therapies fail, introducing the gonadotropins into further algorithms, or the option of ovarian drilling may be considered. In situations where ovulation induction is unsuccessful or additional infertility factors are present, IVF is considered the last option.

In addition to reproductive concerns, women with PCOS often experience a range of dermatological symptoms, compromising predominantly, yet not limited to acne. Acne vulgaris, a persistent low-grade inflammatory skin condition, is common in

both adolescents and adults and can serve as an indication of the underlying hormonal imbalances associated with PCOS. It disrupts the pilosebaceous unit, a critical component for skin health and the regulation of sebum production. Hormonal evaluation plays a key role in guiding treatment decisions, with oral contraceptives being the first-line option for mild androgenic acne. A stepwise, comprehensive approach addressing both the symptoms and root causes of acne ensures improved outcomes for patients, promoting both skin health and overall well-being.

Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

ART	Assisted Reproductive Technique
ASRM	American Society of Reproductive Medicine
CAH	congenital adrenal hyperplasia
CC	clomiphene citrate
CHC	combined hormonal contraceptive
DHEA-S	dehydroepiandrosterone sulfate
DHT	dihydrotestosterone
ESHRE	European Society of Human Reproduction and Embryology
FSH	follicle stimulating hormone
GAGS	global acne grading scale
GnRH	gonadotrophin releasing hormone
HPO axis	hypothalamic-pituitary-ovarian axis
ICSI	intra-cytoplasmic sperm injection
IUI	in utero insemination
IR	insulin resistance
IVF	in vitro fertilization
IVM	in vitro maturation
LH	luteinizing hormone
LOD	laparoscopic ovarian drilling
NTS	neurotensin
OCP	oral contraceptive pills
OHSS	ovarian hyperstimulation syndrome
PCOS	polycystic ovarian syndrome
SERM	selective estrogen receptor modulator

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Chapter 3

Addressing a Key Metabolic Component of PCOS: Insulin

Dawnkimberly Hopkins and Ali Chappell

Abstract

This chapter addresses insulin - a key metabolic component of polycystic ovary syndrome (PCOS), that manifests as insulin resistance and/or hyperinsulinemia, which are prevalent in 65–95% of women with this complex condition. Insulin, insulin resistance, hyperinsulinemia, markers of insulin, and common health conditions associated with their pathophysiology are reviewed. The chapter also concentrates on nutrition as a viable, effective, evidence-based lifestyle option. Common nutritional approaches and the impact they have are presented. A low-insulin lifestyle approach is discussed as an effective intervention for PCOS management. Finally, this chapter presents research that supports the efficacy of a low-insulin lifestyle. Addressing this key metabolic dysfunction is essential for reducing comorbidities and improving the overall quality of health and quality of life in those with PCOS.

Keywords: polycystic ovary syndrome, insulin resistance, nutrition, lifestyle, low-insulin lifestyle, metabolic dysfunction

1. Introduction

PCOS is the most common metabolic-endocrine disorder, affecting individuals from adolescence through post-menopause [1, 2]. This complex, heterogeneous condition consists of multiple signs and symptoms. Although the etiology has not yet been identified, hyperandrogenemia and insulin resistance (IR) are the primary pathophysiological processes that appear to drive PCOS [3]. This chapter discusses hyperinsulinemia as a key metabolic component of PCOS. This chapter will review the physiological and pathological roles of hyperinsulinemia, along with markers used to assess insulin status. It will also discuss common health conditions associated with dysfunctional insulin activity an overview of dietary lifestyle management options will be provided, with an emphasis on low-insulin lifestyle management. Finally, current scientific evidence supporting the effectiveness of a low-insulin lifestyle approach will be reviewed.

2. Insulin

2.1 Physiology

Insulin is a principal anabolic peptide hormone responsible for the metabolic and mitogenic activity of targeted cells in multiple organs. Its intracellular mechanisms

begin with production in the β-cells of the pancreas from the islets of Langerhans, continuing on to partial clearance by liver hepatocytes, followed by delivery and action on vascular endothelium, the brain, muscle fibers, and adipocytes, and ending with insulin degradation in the kidney [4].

Insulin is a modulator of glucose homeostasis. Generally, it is released after ingesting glucose in a process called glucose-induced insulin stimulation. In human cells, glucose transporter 1 (GLUT1) and GLUT3 are the prominent glucose transporters [5]. Once insulin has been released and circulated through the body, it binds to insulin receptors (InsR) on target cell membranes. The InsR is a heterotetrameric receptor tyrosine kinase that is formed by four subunits composed of two extracellular α-subunits and two transmembrane β-subunits [6]. Insulin binding to InsR results in the phosphorylation of insulin receptor substrate (IRS) and the subsequent activation of two primary signaling pathways: the phosphoinositide3-kinase (PI3K)/protein kinase B (Akt) pathway; responsible for the metabolic effects of insulin, such as increased glucose uptake, glycogen synthesis, and protein synthesis, and the mitogen-activated protein kinase (MAPK) pathway; responsible for proliferative and steroidogenic effects [3, 6]. The PI3K/Akt signaling pathway also regulates the translocation of the insulin-sensitive GLUT4 to the membrane of muscle and fat cells for glucose uptake, aiding in glucose homeostasis [5].

In previous studies of lean and obese women with PCOS, cellular and molecular mechanisms of insulin were highlighted, and glucose uptake in insulin target tissues like adipose and skeletal muscles were evaluated [7–9]. It was concluded that although the receptor affinities of insulin are similar in both women with and without PCOS, decreased insulin binding was recorded at the pancreatic β-cell in adipose tissues, resulting in low glucose uptake and insulin sensitivity in women with PCOS compared to those without PCOS. In women with PCOS, as in the general population, the onset of impaired glucose tolerance (IGT) marks a failure of the pancreatic *β*-cell to maintain a state of insulin sensitivity. It is the decreased insulin sensitivity that plagues a large majority of those with PCOS in the form of IR. Insulin resistance in women with PCOS is a major concern due to the negative health outcomes associated with it.

2.2 Pathophysiology

Insulin resistance is defined as an attenuated effect of insulin on blood glucose homeostasis, primarily by less efficient export of glucose from the blood into skeletal muscle, adipose, and liver tissue [10]. Insulin resistance is independent of patients' adiposity, body fat topography, and androgen levels [11, 12]. In PCOS, IR is tissue-selective; skeletal muscles, adipose tissue, and liver lose their sensitivity to insulin, whereas adrenal glands [11, 13], and ovaries remain sensitive [11, 13, 14]. There remains controversy on the direction of cause and effect related to IR and hyperinsulinemia. In diabetic and obesity literature, the dominant paradigm posits that hyperglycemia caused by IR increases β-cell secretion of insulin, resulting in compensatory hyperinsulinemia. On the other side, a framework describes hyperinsulinemia as the primary defect and IR as the protective response of tissues against insulin-induced nutrient overload and metabolic stress [15, 16]. Houston and Templeton presented works to support the view that places IR as the primary defect that causes secondary compensatory hyperinsulinemia, and an alternative framework of hyperinsulinemia as the earlier defect that perpetuates reproductive and metabolic features of PCOS [17]. While debates continue surrounding whether IR or hyperinsulinemia occurs first, the key takeaway for those with PCOS is that there is a dysregulation of insulin causing multiple comorbidities diminishing their quality of health and quality of life.

2.2.1 Hyperinsulinemia

Hyperinsulinemia can both contribute to insulin resistance and arise as a compensatory response to it. It can also develop due to β-cell proliferation or heightened responsiveness of β-cells to nutrient stimulation, potentially driven by chronic overnutrition, triggering increased postprandial insulin secretion [18]. Hyperinsulinemia in the fasted state can arise from inability to regulate basal secretion, resulting in sustained hyperinsulinemia without glucose stimulation [19]. Elevated insulin levels without concurrent IR have been observed in lean PCOS patients. Vrbíková and his colleagues described lean PCOS subjects with higher early-phase glucose-stimulated insulin secretion than controls. They found that lean PCOS subjects had elevated fasting insulin despite normal insulin sensitivity in hyperinsulinemic euglycemic clamps [20]. This point is critical, as later in the chapter, we will discuss a low-insulin lifestyle approach aimed at addressing the harmful effects of elevated insulin levels in individuals with PCOS—shifting the focus from weight management to metabolic health.

3. Insulin markers

As we shift the focus to metabolic health, evaluation and monitoring of physiological events influenced by insulin activity are essential. When evaluating the influence of insulin on those with PCOS, the use of insulin as an assessment marker is not typically supported, but rather markers for IR. When considering monitoring insulin levels, Kahn and colleagues suggested PCOS insulin secretion should always be examined in the context of peripheral insulin sensitivity rather than in isolation [21]. Kahn and colleagues also highlight an important issue: the interpretation of serum insulin levels, both fasting and post-glucose stimulation. The liver plays a central role in maintaining glucose and insulin homeostasis. In insulin-resistant individuals, such as those with PCOS, it becomes challenging to assess not only the pancreas' compensatory capacity but also the influence of hepatic, renal, and peripheral tissue insulin clearance on circulating insulin levels. In light of these challenges, insulin alone has not been clinically accepted as a practical assessment, however, researchers contend that rapid and fast glucose analyses enable them to evaluate IR. For this purpose, homeostatic model evaluation (HOMA), quantitative insulin sensitivity check index (QUICKI), and fasting glucose and insulin levels have been established and utilized in clinical research and metabolic investigations of insulin activity in PCOS [22–25]. Although these measures are commonly used to evaluate IR, it is worth noting that IR is known to precede the development of abnormal blood sugar levels and/or abnormal HbA1c levels for decades [26]. For this reason, early insulin evaluation is critical for early identification and prevention of IR. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is an appealing approach for the analysis of insulin because this platform has the capacity to distinguish insulin, proinsulin, C-peptide, and many insulin analogs; unlike immunoassays which come with certain limitations [27]. A significant limitation of immunoassays is that it relies on antibodies for detection which can suffer from non-specificity due to antibody cross-reactivity with proinsulin or partially processed forms of proinsulin [28]. LC-MS/MS technology is a proven and increasingly widespread method that should be considered in clinical use for assessment of insulin levels in women with PCOS.

Whether due to IR or hyperinsulinemia, assessing insulin activity is essential, given its wide-ranging impact. Insulin dysregulation plays a significant role in the

cardiometabolic, endocrine, and reproductive manifestations of PCOS. In the following section, we will discuss common comorbidities closely linked to insulin dysregulation of IR.

4. Comorbidities linked to insulin resistance

4.1 Inflammation, dyslipidemia, hypertension, and cardiovascular disease

Studies have established PCOS as a pro-inflammatory condition marked by chronic low-grade inflammation [29, 30]. Women with PCOS have higher levels of inflammatory markers like C-reactive protein (CRP), leukocytes/white blood cells (WBCs), certain interleukins such as IL-6 and IL-18, and tumor necrosis factor (TNF) [30]. Chronic low-grade inflammation has been associated with obesity, metabolic syndrome, dyslipidemia, hypertension (HTN), endothelial dysfunction, and atherosclerosis, placing those with PCOS at higher risk for long-term metabolic sequelae, such as type 2 diabetes (T2D) and cardiovascular disease (CVD) [31, 32].

Dyslipidemia, the most prevalent metabolic abnormality in PCOS, along with endothelial dysfunction, an early sign of subclinical atherosclerosis, contributes to higher systolic and diastolic BP, making HTN a common clinical concern in these patients [33]. The typical profile of dyslipidemia in PCOS includes decreased HDL cholesterol, increased LDL cholesterol and triglyceride levels [34]. Endothelins are a family of peptides involved in many physiological processes. These processes are linked to several vascular diseases, including as stated above, HTN. Endothelin-1 (ET-1) is a vasoconstrictor peptide that can contribute to vascular structural changes, including thickened artery walls and remodeling and lengthening of small arteries their involvement in PCOS was suggested by the observation that obese and non-obese women with PCOS have higher levels of circulating ET-1 compared with controls [35]. It has been found that hypertensive patients have elevated plasma ET-1 concentrations. Xu and colleagues conducted a meta-analysis that included 450 hypertensive patients and 328 controls and found a potential link between increased ET-1 activity and the development of hypertension. From these findings, Xu and colleagues postulate that it is highly likely that the elevated plasma ET-1 concentrations in hypertensive patients are secondary to HTN and may reflect endothelial cell damage [36].

The causal relationship between aldosterone and IR/hyperinsulinemia remains unclear; Krug and Ehrhart-Bornstein found that hyperinsulinemia is associated with increased aldosterone levels which leads to water retention through complex mechanism impacting sodium and potassium balance potentially contributing to hypertension [37]. Conversely, Colussi and colleagues found that aldosterone itself can worsen insulin resistance, contributing to a cycle of increased aldosterone and HTN [38].

4.2 Obesity

Although there are lean profiles of PCOS, approximately 87.5% of women with PCOS are overweight and 65% are obese [39]. Scientists continue to explore the link between obesity and PCOS, as the exact cause-and-effect relationship remains unclear. While obesity-especially excess visceral and subcutaneous abdominal fat, can worsen PCOS symptoms by increasing insulin resistance, disrupting hormone balance, and contributing to significant metabolic issues, studies have indicated that

it may not be the primary driver of PCOS [15, 30, 40]. The trajectory of weight gain in women with PCOS is a major concern personally and clinically, as phenotypical central obesity-fat around the midsection, worsens IR and PCOS symptoms [29, 41].

4.3 Metabolic syndrome

Polycystic ovary syndrome can be seen as the female-specific form of metabolic syndrome (MetS). Like PCOS the pathophysiology of MetS encompasses several complex mechanisms that are yet to be fully elucidated. Also similar to PCOS, proposed mechanisms, IR, chronic inflammation, and neurohormonal activation are essential players in the progression of MetS and its subsequent transition to CVDs and T2DM [42]. As a syndrome, according to the consensual definition of the International Diabetes Federation, the American Heart Association, and the National Heart, Lung and Blood Institute, MetS is characterized by a clustering of metabolic risk factors, which is defined by the simultaneous occurrence of at least three of the following components: (a) central obesity, (b) dyslipidemia, (c) impaired glucose metabolism, (d) elevated blood pressure (BP), and (e) low levels of high-density lipoprotein cholesterol (HDL-c) [43]. All of the necessary components for Mets are commonly present in PCOS. It is not surprising that the results of a meta-analysis of all studies that assessed the prevalence and risk of MetS in PCOS, regardless of age groups and different methods of confounder control, showed that the odds of MetS among women with PCOS were 2.5-fold higher than in healthy controls [44].

4.4 Diabetes and gestational diabetes

Impaired glucose tolerance, pre-diabetes, diabetes, and gestational diabetes (GDM) are all common metabolic conditions in PCOS. Insulin levels are higher in women with PCOS, which raises their risk of these conditions [45]. Increased insulin levels in early pregnancy (before gestation week 16) are strong predictive factors for GDM by gestational weeks 32–34 [46]. Insulin resistance is a hallmark feature of PCOS. Epidemiological studies have established a strong link between PCOS and an elevated risk of type 2 diabetes, IGT, and GDM. A meta-analysis found that women with PCOS are approximately three times more likely to develop these conditions [47–49].

4.5 Infertility

Reproductive physiology is a complex and delicate interplay of the hypothalamic-pituitary-ovarian (HPO) axis. Interactions that disturb the balance of these elements cause metabolic and reproductive disorders, as seen in PCOS. Women with PCOS are at an increased risk of infertility due to hormonal imbalances related to irregular ovulation or anovulation, which can make it difficult to conceive. Starting from the hypothalamus, gonadotropin-releasing hormone (GnRH) triggers the release of the gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These gonadotropins exert their action on the ovaries to stimulate follicular growth and ovulation [50]. In PCOS, hyperinsulinemia and hyperandrogenemia play major roles in disruptions to this process by inhibiting follicle growth and, ultimately, ovulation [51, 52]. Additionally, elevated insulin levels are toxic to early placental growth leading to increased risk of miscarriage [53]. While PCOS is a chronic condition, it's often treatable, and many women with PCOS can still become pregnant with treatment.

4.6 MASLD

Metabolic dysfunction-associated steatotic liver (MASLD) previously known as Nonalcoholic fatty liver disease, or NAFLD, is a chronic condition in which fat accumulation occurs in the liver, and is histologically identical to alcoholic liver disease, in patients with no or minimal alcohol consumption [54]. MASLD is a significant contributor to adverse health outcomes due to its potential progression to end-stage liver disease. Insulin resistance plays a key role in the development of this condition, with numerous studies demonstrating a strong association between the two conditions. The prevalence of MASLD is elevated in individuals with obesity, type 2 diabetes, and dyslipidemia—conditions that are also commonly seen in PCOS [55]. Research indicates that MASLD is the hepatic manifestation of metabolic syndrome and that it is highly prevalent among women with PCOS [56, 57].

4.7 Mental health disorders

It is well known that PCOS is associated with a high prevalence of depression and anxiety [58]. No specific mechanism of etiology has been identified, but there are multiple factors that are suggested to play a role. Hyperandrogenemia manifesting as increased body and facial hair, male pattern balding and cystic acne can impact self-esteem and body image. Overweight and obesity, which are present in 65–87% of those with PCOS can also impact self-esteem and body image leading to decreased quality of life [39]. As previously mentioned, visceral adiposity, in particular, contributes significantly to the low-grade inflammatory state of PCOS by producing the cytokines, tumor necrosis factor alfa (TNF-α), Interlukin-6 (IL-6), and interlukin-18 (IL-18), chemokines, and other adipokines, which may also contribute to increased association of mental disorders present in PCOS [30]. Additionally, inhibitory neurotransmitters such as serotonin (5-HT), dopamine (DA), gamma-aminobutyric acid (GABA), and acetylcholine (Ach) are diminished in PCOS [59]. Although there are data to support neuroendocrine involvement in PCOS, there is a lack of neuroimaging studies investigating those processes. Saydam and Yildiz (2021), published a mini review discussing the relevance of central nervous system imaging modalities in understanding the neuroendocrine pathophysiology of PCOS as well as their relevance to understanding its comorbidities. Twelve neuroimaging studies were identified between 2011 and 2020 (Three investigated structural differences and nine investigated functional disturbances). Structural differences via magnetic resonance imaging (MRI) and Functional disturbances via functional magnetic resonance imaging (fMRI) and positron emission tomography and computed tomography (PET CT) provided insight into clinical implications of IR in women with PCOS. Insulin resistance implications included: (a) decreased global and regional brain volumes, (b) altered white matter microstructure, (c) diminished reward response in corticolimbic areas, (d) brain glucose hypometabolism, (e) greater μ-opioid receptor availability in reward related regions, and (f) increased activation during memorial and emotional tasks. Clinical implications due to the presence of IR manifested as: (a) increased non-homeostatic eating, (b) diminished appetitive responses, (c) cognitive dysfunction, and d) mood disorders [60].

Psychological health in PCOS has been neglected as a condition that requires evaluation in the same manner as all the other comorbidities present in PCOS. The Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome suggest healthcare

professionals should be aware of the high prevalence of moderate to severe depressive symptoms, depression and anxiety in adults and adolescents with PCOS and should screen for these conditions in all adults and adolescents with PCOS, using regionally validated screening tools [61].

The high prevalence of comorbidities present in PCOS indicates that this condition should be considered a general health problem related to insulin dysregulation rather than primarily a reproductive condition. Whether cause or consequence, there is a critical need to address both hyperinsulinemia and IR in PCOS, where it is worth noting again that 65–95% of those with PCOS suffer from this condition, which includes lean, overweight and obese individuals. The current era of anti-obesity therapy offers pharmacologic tools to improve metabolic, reproductive, and other clinical outcomes in a subset of patients who are overweight or obese, primarily through weight reduction [62]. However, shifting the focus from weight-related issues to the metabolic effects of insulin—as the primary pathophysiological factor influencing individual PCOS phenotypes—is essential for improving the management of all patients with PCOS. As we consider interventions that are inclusive of all PCOS phenotypes, the next section will focus on nutrition and the role it plays in lifestyle management.

5. Nutrition as a viable intervention

Nutrition plays a critical role in the management of PCOS, yet typical dietary recommendations often focus primarily on weight loss without addressing the root problem: elevated insulin levels and IR [63, 64]. Patients are often told to simply "eat less and exercise more," but this approach overlooks how certain foods uniquely affect hormonal regulation, especially insulin [65, 66]. Rather than focusing on calorie reduction, nutritional strategies for PCOS should aim to reduce insulin levels and improve metabolic flexibility. A more effective approach begins with understanding how different foods impact insulin levels, not just calories or macronutrient ratios. This approach is called a low-insulin lifestyle [67].

Lifestyle change is well accepted as a first-line treatment, but those with PCOS often find their efforts frustrating and unsuccessful. While they may attempt calorie restriction, portion control, or increased physical activity, these strategies do not always lead to meaningful improvements, especially when insulin resistance is unaddressed. The issue is often not a result of a lack of willpower or effort, but that traditional weight loss recommendations fail to appreciate the central role that insulin plays in driving PCOS symptoms. Addressing insulin directly, rather than focusing solely on weight, offers a more effective and targeted strategy for improving outcomes.

6. Why insulin should be the primary focus in PCOS

Chronically elevated insulin is one of the key drivers of nearly every symptom associated with PCOS [68, 69]. It contributes to increased androgen production, irregular ovulation, weight gain, acne, and hirsutism. Elevated insulin also suppresses sex hormone-binding globulin (SHBG), increasing the amount of free testosterone circulating in the body. Lowering insulin can help reverse these effects, restoring ovulation, improving skin, reducing cravings, and improving mood and energy. Whether a woman is lean or overweight, focusing on lowering insulin levels is the most effective way to improve both metabolic and reproductive outcomes [70, 71].

7. Dietary approaches and their impact on insulin

7.1 Low fat

Low-fat diets were long considered the gold standard for heart health and weight loss. In PCOS, they are sometimes recommended with the goal of reducing overall calorie intake. However, studies have not found diets low in fat to be successful for long-term weight loss, most likely because these diets often lead to increased consumption of sugar, starch, and processed low-fat products that can spike insulin levels [72]. For individuals with PCOS, this can be counterproductive. Dietary fat plays an important role in hormone production, skin and hair health, and satiety [73]. When fat is removed from the diet, it often leads to increased hunger, cravings, and nutrient deficiencies that can worsen PCOS symptoms.

Rather than avoiding fat, the focus should shift to choosing the right types of fats. Those with PCOS should be encouraged to include plenty of healthy fats from whole food sources like avocados, nuts, seeds, olive oil, coconut, and fatty fish. These fats help increase satiety, promote hormonal balance, and support long-term metabolic health without triggering excessive insulin release.

7.2 Low carbohydrate and ketogenic diets

Low carbohydrate and ketogenic diets are also often recommended for individuals with PCOS. These dietary approaches have been shown to improve metabolic and cardiovascular biomarkers compared to low fat diets [72, 74]. However, low-carb does not always mean low insulin. Certain proteins, such as whey and casein, can still cause a major insulin spike, even though these products are free of carbs. This is because they are highly concentrated in branched chain amino acids (BCAAs), which are potent insulin-spiking amino acids. These BCAAs not only lead to a significant insulin spike, but they also increase insulin-like growth factor one (IGF-1), which is associated with worsened PCOS symptoms such as acne and hirsutism, in addition to other health concerns [12–16, 75–79]. Since whey protein powder is now added to everything from protein bars to pancakes, it could potentially be causing more problems than people realize [80–83].

The ketogenic diet is a very low-carb, high-fat diet, drastically limits fruit and vegetables, which can impact gut health, nutrient intake, and long-term sustainability. Since low-carb and ketogenic diets require consistent carbohydrate tracking, they can often lead to burnout, which is why they are usually difficult to sustain. They can also lead to food obsession and binge eating as people struggle to track macronutrient intake, which could potentially do more harm than good mentally, especially for those already navigating hormonal issues.

7.3 Mediterranean

The Mediterranean diet is often recommended for its heart health benefits and anti-inflammatory approach. It emphasizes fruits, vegetables, whole grains, legumes, olive oil, nuts, seeds, and fish. Some studies have shown that the Mediterranean diet can improve menstrual regularity and reduce inflammation in PCOS. However, the inclusion of whole grains and legumes, foods high in starch, while perhaps beneficial for the general population, can potentially lead to excessive insulin stimulation in those with severe IR [84, 85]. Additionally, while a Mediterranean diet approach may benefit individuals with mild IR or those

transitioning off a standard Western diet, it may not go far enough for individuals with hyperinsulinemia or severe PCOS symptoms. Instead, a focus on healthy fats, non-starchy vegetables, whole fruits, nuts, seeds, and fish without the grains and legumes may be an approach that provides all the benefits of a Mediterranean approach, without excess starch [86, 87].

7.4 Paleo

The Paleo diet emphasizes whole, unprocessed foods and excludes grains, legumes, dairy, and refined sugars. It can be naturally lower in insulin spiking foods and has gained popularity among those with PCOS for its emphasis on protein, vegetables, nuts, and healthy fats. However, depending on how it is implemented, Paleo can be high in sugar and starch if excessive amounts of starchy tubers, honey, or maple syrup are consumed, as well as modern processed starches such as tapioca and cassava which are often added to paleo processed foods.

Additionally, the exclusion of all dairy may limit options that could be included thoughtfully in an insulin-lowering approach. Fermented dairy products, like full-fat Greek yogurt and aged cheeses, contain little to no whey, which is the portion of dairy most responsible for insulin spikes. Fermentation also alters the structure of the proteins, from BCAAs to branched chain keto acids (BCKA), reducing their insulinogenic impact [88, 89]. When included in limited amounts, they can provide beneficial nutrients like calcium and probiotics, without significantly affecting insulin levels [90].

7.5 Plant-based

Plant-based diets, including vegetarian and vegan, are often recommended to improve overall metabolic health. These diets are rich in fiber, antioxidants, and anti-inflammatory foods. However, many plant-based diets are high in starches like grains, beans, and potatoes, which can be problematic for individuals with IR [84, 85, 91]. It's possible to follow an insulin-friendly, plant-based diet, but it requires focusing on non-starchy plant-based proteins, such as edamame, tofu, tempeh, lupini beans, and hemp seeds. These protein options can help ensure you get enough protein without the starch. For those who follow a vegetarian diet, including eggs and fermented dairy products provide additional protein options.

8. What is a low-insulin lifestyle

Unlike traditional dietary recommendations, a low-insulin lifestyle specifically focuses on limiting foods that cause excessive insulin secretion. It focuses on the insulin response to certain foods rather than carbohydrate or calorie content [86, 92–95].

This lifestyle is ideal for individuals with PCOS because it targets hyperinsulinemia directly. Since up to 95% of patients with PCOS have chronically elevated insulin levels, limiting foods that are known to elicit excessive insulin response is ideal for lowering insulin levels, reversing IR, and improving metabolic and reproductive health. Instead of chasing weight loss, this approach helps facilitate weight loss by improving appetite regulation and improving energy levels.

A low-insulin lifestyle emphasizes lean meats, poultry, eggs, and fatty fish, which supply protein without the excessive insulin-spiking effects of whey or casein [67]. Non-starchy plant-based proteins, such as edamame, tofu, tempeh, hemp seeds, and

lupini beans, offer alternatives for those following vegetarian or plant-based diets. Non-starchy vegetables, like leafy greens, cruciferous vegetables, peppers, carrots, tomatoes, and cucumbers, are the foundation of this approach due to their minimal insulin impact and high nutrient density. Whole fruits are included as well; while they contain natural sugars, the fiber content slows absorption and the fructose component does not directly trigger insulin secretion. Healthy fats from sources like avocados, olives, coconut, nuts, and seeds, along with olive, avocado, or coconut oil, are a critical part of this approach. These fats support hormone production, promote satiety, and help stabilize blood sugar without stimulating insulin. Fermented dairy products, such as full-fat Greek yogurt and aged cheese, may be included in limited amounts (e.g., up to 1 serving per day total).

While certain foods are considered "healthy" by conventional standards (e.g., whole grains, beans and legumes, and sweet potatoes), they may still drive chronic insulin elevation [84, 85]. Below are the three most critical food categories that are limited or avoided on a low-insulin lifestyle due to their strong insulin-stimulating effects:

8.1 Starches

Starches are long chains of glucose molecules. Once consumed, the body quickly breaks these chains down into glucose, which is rapidly absorbed into the bloodstream. This rise in blood glucose stimulates a sharp rise in insulin [91, 96]. Starches include foods like bread, pasta, rice, potatoes, oats, corn, and grain-based flours as well as starchy vegetables, such as sweet potatoes. While many nutrition guidelines recommend starches as a core part of a balanced diet, these foods are often counterproductive for someone trying to lower insulin levels.

In addition, modern starches differ from ancient forms in several important ways. Over thousands of years, agricultural practices have selectively bred grains, corn, and potatoes to be larger and sweeter, optimizing them for their starch content while reducing their fiber content. As a result, today's starches are not only more insulin-spiking, but they also lack the natural buffering effect that higher fiber content was meant to provide [97–99].

The way we cook starches worsens this effect. Most starchy foods are boiled, baked, mashed, or otherwise cooked in ways that increase their *gelatinization* [96]. Gelatinization is a process in which starch granules absorb water and swell, making them easier to digest. While this improves taste and texture, it also makes the starch much more accessible to digestive enzymes, which means it is broken down and absorbed even faster, leading to a more rapid and pronounced insulin spike.

Even so-called "whole grain" products are often finely milled or processed, removing much of the intact fiber structure that would otherwise slow digestion. And while starchy vegetables like sweet potatoes or corn do offer some vitamins and minerals, it's important to recognize that all of the essential nutrients found in these foods can also be found in non-starchy vegetables and fruits. The difference is that non-starchy produce offers these benefits without the same degree of insulin stimulation [85].

8.2 Added sugars

It's well known that sugar is one of the most potent stimulators of insulin. This includes not only table sugar but also honey, maple syrup, agave, coconut sugar, and even so-called "natural" sweeteners like fruit juice or date syrup. These sugars are rapidly absorbed and drive a sharp insulin response, even in small amounts.

Chronically elevated insulin drives frequent hunger and intense cravings, especially for sugary, processed foods. The more sugar consumed, the more insulin is released, creating a cycle that's hard to break [66]. Unfortunately, many foods marketed as healthy still contain hidden sugars, keeping insulin levels elevated throughout the day. A low-insulin lifestyle removes or strictly limits added sugars, helping to break this cycle. It encourages whole foods and allows for occasional use of non-insulinogenic sweeteners like erythritol, allulose, monk fruit extract, or stevia.

8.3 Dairy

Milk is a food designed by nature to promote rapid growth [100, 101]. It naturally contains both insulin and insulin-like growth factor 1 (IGF-1), two powerful growth promoting hormones. These play an important role in milk's biological purpose: to help newborn mammals grow quickly during their earliest stage of life. While this is beneficial for infants, chronically elevated insulin and IGF-1 can be problematic in adults, especially those with PCOS [77, 102].

In addition to the hormones naturally present in milk, dairy proteins, particularly whey, are highly insulinogenic [80, 82]. This means they stimulate a significant insulin response, even when there's very little carbohydrate or sugar involved. In fact, whey protein is one of the most insulin-stimulating components of the human diet. Clinical studies have shown that whey triggers a strong insulin release independent of its effect on blood glucose [80]. Considering the widespread use of whey protein among food products, often marketed as "high protein," this may have unintended consequences. It is a potentially hidden contributor to chronic hyperinsulinemia in susceptible individuals.

For individuals with PCOS, this is especially concerning. High insulin levels are already a key driver of hormonal imbalance, and regular consumption of insulin-stimulating dairy products can further worsen the cycle. Elevated insulin promotes increased androgen production, disrupts ovulation, and contributes to acne, hirsutism, and irregular menstrual cycles.

Dairy also increases circulating levels of IGF-1, a hormone that shares structural similarities with insulin and stimulates cell growth and hormone production [77, 103]. In women with PCOS, who are already prone to elevated androgens and acne, increased IGF-1 can worsen these symptoms. Numerous studies have linked dairy consumption with higher IGF-1 levels and an increased risk of acne and symptoms of hormonal imbalance [95, 104–106].

However, not all dairy products affect the body in the same way. Fermented dairy products like full-fat Greek yogurt and aged cheeses undergo a bacterial fermentation process that alters the protein structure and reduces their insulin stimulating properties [88–90]. Because of this, a low-insulin lifestyle allows for limited consumption of full fat Greek yogurt and aged cheese.

Importantly, there is no nutrient in dairy that cannot be obtained elsewhere. Calcium, potassium, vitamin D, and protein can all be found in other whole foods like leafy greens, chia seeds, almonds, and fortified non-dairy milks as well as fermented dairy products.

9. Scientific evidence supporting a low-insulin lifestyle

Multiple clinical trials have evaluated a low-insulin lifestyle as an intervention for PCOS and found consistent improvements in insulin sensitivity, menstrual function, and weight reduction [86, 92–94].

Studies using this approach have reported up to a 52% reduction in fasting insulin, with improvements in both HOMA-IR and QUICKI scores observed in just 8 weeks. Across three prospective clinical trials, including one randomized controlled trial comparing the approach to standard care plus metformin, participants lost an average of 12 to 19 pounds in 8 weeks without pharmacologic intervention. These trials also documented increases in fat oxidation, indicating improved metabolic flexibility and an improved ability to utilize fatty acids for energy. Despite their short duration, the studies showed significant reductions in hemoglobin A1c, as well as marked improvements in triglyceride levels and free testosterone, key markers of cardiometabolic and reproductive health in PCOS. Together, these results highlight the rapid and multisystem benefits of reducing insulin through targeted nutritional intervention.

In addition to biomarker improvements, participants experienced reductions in acne, mood stabilization, more consistent energy, and fewer cravings. A case series also documented spontaneous pregnancies in individuals who had previously experienced infertility [92]. Couples conceived on average 86 days of starting a low-insulin lifestyle approach.

Most recently, a systematic review and meta-analysis further supported these findings, concluding that low insulin dietary strategies are effective for improving metabolic parameters and reproductive outcomes in PCOS [95].

10. Conclusion

This chapter has provided a brief overview of the physiology and pathophysiology of insulin, as well as common markers used in the evaluation of insulin status within PCOS. Metabolic dysfunctions characterized in the various comorbidities that exist in PCOS were presented. These comorbidities stress the need to consider PCOS as metabolic disorder and not primarily a reproductive condition. Given its prevalence and the impact it has on health and quality of life in lean, overweight and obese individuals with this condition; a narrative shift is necessary. Rather than centering care around weight management, the focus must shift toward improving metabolic health and addressing the root driver: elevated insulin levels. Early screening for hyperinsulinemia is critical, as it allows for timely intervention before more severe symptoms and complications develop. A low-insulin lifestyle offers a targeted, evidence-based, and sustainable approach that addresses hyperinsulinemia directly. Multiple prospective trials have demonstrated its ability to significantly improve weight, insulin sensitivity, and hormonal balance, without the need for medications. This lifestyle approach has the potential to be a meaningful part of the solution for improving the health and quality of life for individuals with PCOS.

Conflict of interest disclosure

Ali Chappell is the Founder and CEO of Lilli Health, a digital health company focused on providing education for individuals with insulin resistance and PCOS.

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Chapter 4

Urological Associations and Sequalae of PCOS: Urinary Stones, Kidney Disease, Lower Urinary Tract Symptoms and Infections, and Fowler's Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder with primary effects on reproductive health, but its systemic impact extends beyond the ovaries. Emerging evidence highlights significant urological associations of PCOS, linking it to various lower urinary tract and renal conditions. This chapter explores the interplay between hormonal imbalances, insulin resistance, metabolic syndrome, and chronic inflammation in shaping the urological sequelae of PCOS. Key topics covered include the increased prevalence of lower urinary tract symptoms (LUTS), overactive bladder (OAB), urinary tract infections (UTIs), and nephrolithiasis in women with PCOS. Insulin resistance and obesity contribute to urinary stone formation, urinary frequency, and pelvic floor dysfunction, which may exacerbate stress urinary incontinence (SUI). Additionally, evidence suggests that chronic inflammation and hormonal dysregulation may predispose PCOS patients to bladder pain syndrome/interstitial cystitis (BPS/IC) and even early kidney dysfunction. A dedicated section in this chapter will also explore Fowler's syndrome, a rare but important cause of urinary retention in young women, which has been linked to PCOS. Fowler's syndrome is characterized by detrusor underactivity and abnormal sphincter electromyographic activity, often presenting in women with hormonal disturbances. Understanding this relationship is crucial for improving the diagnosis and management of PCOS-related urological dysfunction. This chapter aims to bridge the gap between endocrinology, urogynecology, and functional urology, offering a comprehensive perspective on how PCOS affects urinary health. By highlighting these associations, we hope to improve awareness, promote early identification, and guide targeted management strategies for affected women.

Keywords: PCOS, urology, Fowler's syndrome, lower urinary tract symptoms, kidney stones, urinary tract infections

1. Introduction

Polycystic ovarian syndrome (PCOS) is a common systemic condition in adolescent females primarily characterized by metabolic, endocrine, and reproductive manifestations. Metabolic features manifest in mainly obesity and insulin resistance. Endocrine features include cutaneous signs of hyperandrogenism, such as hirsutism and acne, while reproductive features involve mainly ovulatory dysfunction, menstrual irregularity, and polycystic ovarian morphology [1].

PCOS has lifelong consequences in the short and long terms. Women with PCOS have increased risk for obesity, infertility, sleep apnea, psychological and mental health disturbances, abnormal lipid levels as well as non-alcoholic fatty liver disease. These in the long term can lead to diabetes mellitus, endometrial cancer, and cardiovascular disease [1].

While PCOS is primarily a gynecological disorder, it also has urological associations. The combination of hormonal imbalances, insulin resistance, metabolic disturbances, and pelvic floor dysfunction all play a role in causing urinary symptoms in women with PCOS [2]. This leads to increased susceptibility to urinary tract infections (UTIs), urinary urgency, frequency, incontinence, pelvic pain, and kidney stones (**Figure 1**) [3].

2. Pathophysiological links between PCOS and urological disorders

Polycystic ovarian syndrome (PCOS) is a spectrum classically represented with the following: hormonal imbalances, menstrual dysfunction, polycystic ovaries, insulin resistance, as well as PCOS-associated comorbidities, such as metabolic syndrome and obesity [4]. Its pathophysiology has a complex interplay between intrinsic and extrinsic factors, which cross pathways with urological disorders. Intrinsic factors include genetic and epigenetic variants in the mechanisms regulating hormonal secretion and action. Estrogen, progesterone, and testosterone influence the urinary system and contribute to the development of urological disorders. Extrinsic factors include

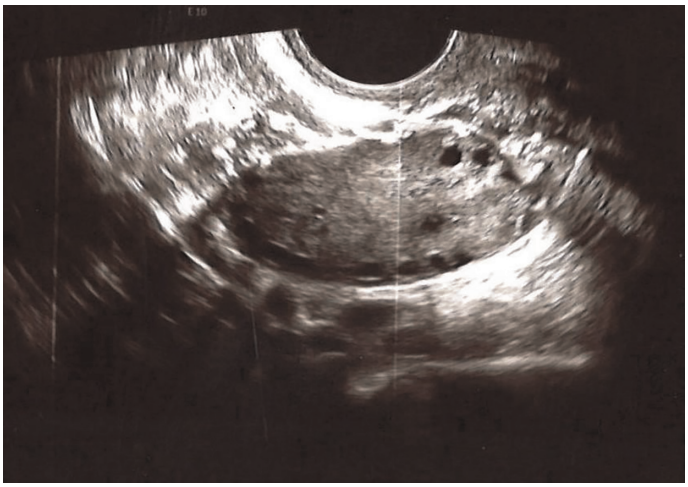

Figure 1.
Transvaginal sonography displays multiple small hypoechoic cysts. (Reproduced with permission) (Copyright of Dr. Layali Aldaihani.)

environmental factors that promote obesity and insulin resistance, which are correlated with several urological disorders discussed in this chapter [5].

Despite the extensive research, the genetics of PCOS remain a subject of investigation. Ruth and colleagues studied human genetics to try and understand the impact of testosterone on disease development in both genders. They concluded that a one standard deviation increase in testosterone level increased the risk of developing PCOS by 1.5 times [6]. In another study, Day et al. [7] identified statistically significant associations between PCOS and three novel genetic loci: PLGRKT, ZBTB16, and MAPRE1. The first gene codes for a plasminogen receptor, and variants of this gene may result in chronic inflammation and contribute to the pathophysiology of PCOS. The second and third genes code for proteins that are involved in ovarian follicle development. Variants of these two genes may contribute to ovarian dysfunction seen in PCOS. Furthermore, the large-scale genome-wide meta-analysis performed by Day et al. replicated associations at 11 previously reported loci with PCOS [7].

Epigenetics demonstrate variations of gene expression with an intact genetic code [8]. Mimouni et al. [9] studied the role of DNA methylation in regulating key genes associated with PCOS. They exposed a group of pregnant mice to high levels of anti-Mullerian hormone (AMH) during the critical gonadal sex determination period and studied their offspring for long-term disease outcomes. The exposed group was matched with a control group that underwent parallel breeding. Each group was studied over four generations. Although only the first generation were directly exposed to AMH, PCOS-like characteristics were documented in subsequent lineages, including persistent elevation in both testosterone and LH levels, as well as ovarian histological analysis consistent with oligo-anovulatory phenotype. Furthermore, RNA sequencing and genome-wide DNA methylation profiling of ovarian tissue from the control group and the group with third-generation PCOS-like mice were conducted. A hundred and two differentially expressed genes were identified in the AMH exposed third-generation ovaries compared to controls. The upregulated genes were linked to ovarian function, insulin metabolism, and angiogenesis, whereas the downregulated genes were related to epigenetic modifications, cell growth, and apoptosis. This supports epigenetic transgenerational inheritance of PCOS [9].

The role of estrogen in the genitourinary tract is well documented. The bladder, urethra, and pelvic floor express estrogen receptors, suggesting their involvement in mediating urinary tract symptoms. Estrogen acts on muscarinic receptors and inhibits calcium ion channels in muscle cells, reducing detrusor overactivity. It increases urethral resistance and closure pressure, which promotes continence. Estrogen also directly affects collagen synthesis in the lower urinary tract. It contributes to the formation of antimicrobial peptides, which protect the urothelium against bacterial infections. It supports cell to cell contact-associated proteins, which reinforce the epithelium against microbes. Therefore, the lack of estrogen can lead to stress urinary incontinence, urogenital prolapse, urinary frequency, urinary urgency, nocturia, reduced bladder capacity, and recurrent urinary tract infections. Although the literature on lower urinary tract symptoms in PCOS is limited, studies have shown that 70% of postmenopausal women, whom are in a state of hypoestrogenism, complain of lower urinary tract symptoms. In addition, their symptoms improved with vaginal estrogen by 40 to 75% [10, 11].

Dr. Clare J. Fowler first described the effects of progesterone deficiency on the genitourinary tract. PCOS patients have progesterone deficiency due to disrupted ovulation. On a molecular level, progesterone acts on stabilizing cell membranes. Its absence allows impulse transmission between the muscle fibers in the urethral sphincter and impairs sphincter relaxation. This was depicted as abnormal electromyographic activity of the external urethral sphincter. It can result in incomplete

urinary bladder emptying and urinary retention in PCOS-affected patients [12]. Szymański and colleagues reviewed the succeeding literature and found consistent results regarding the effects of progesterone deficiency on the urethral sphincter [13].

Another key influencer on the urinary tract is hyperandrogenism, which is quintessentially implied by the presence of androgen receptors in the urinary bladder, urethra, and pelvic floor. Hyperandrogenism stimulates protein synthesis and increases the pelvic muscle mass. It demonstrated a protective effect against stress urinary incontinence in animal studies. Despite this, PCOS-affected individuals have significantly higher rates of urinary incontinence compared to controls [3, 14, 15]. This discrepancy between animal and human models may be attributed to the higher incidence of obesity and underlying inflammation seen in PCOS [16, 17].

Metabolic syndrome is 3.5 times more common in PCOS, and up to 88% of PCOS-affected patients suffer from obesity [18, 19]. Uzun and colleagues studied the association between insulin resistance and overactive bladder (OAB) and found a positive correlation. A multivariate regression analysis was implemented and confirmed insulin resistance is an independent risk factor for OAB [20]. Hsu et al. [21] reviewed articles and identified common denominators in the shared pathophysiology between metabolic syndrome and OAB. These included an altered autonomic nervous system, chronic ischemia, chronic proinflammatory state, dysregulated nutrient-sensing pathways, and dysbiosis, which resulted in urinary bladder denervation, fibrosis, and afferent oversensitivity [21]. This can be further explained by the bladder–brain–gut axis. There is an open communication involving neurotransmitters and hormonal signaling between all three organs. Since metabolic syndrome and obesity are driven by a cycle of unhealthy eating and insulin resistance, large intake of low nutrient dense, high caloric, highly refined foods, and a sedentary lifestyle can cause the translocation of gut and urinary microbiomes. This translocation produces metabolites that influence the brain, bladder, and gut function and promotes a state of chronic low-grade inflammation in the body [19, 22]. Jung and colleagues expanded more on the bladder and brain–gut axis. They noted irritable bowel syndrome is the second most common comorbidity in patients with interstitial cystitis. Additionally, urinary incontinence is not uncommonly found along with fecal incontinence. Moreover, psychological stress exacerbates the urological symptoms in patients suffering from OAB and interstitial cystitis [22–24]. Hence, it can be deduced that metabolic disorders in PCOS can perpetuate the development of urological symptoms [19, 21–24].

3. Lower urinary tract dysfunction (LUTD) in PCOS

The term lower urinary tract symptoms (LUTS) refers to a range of symptoms affecting the function of the bladder and urethra. These symptoms are mainly characterized into storage symptoms, such as frequency and urgency, voiding symptoms, such as hesitancy, dribbling and straining, and post-voiding symptoms, such as incomplete bladder emptying [3].

Overactive bladder (OAB) is an idiopathic disorder defined as symptoms of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology [25]. Women with PCOS may experience symptoms of OAB, and this may be caused by hormonal factors like elevated androgen levels or insulin resistance. Studies found that women with higher serum testosterone levels are more prone to report symptoms of urgency, nocturia, and pelvic pain. These hormonal changes can impact the urinary tract

by contributing to urinary frequency, urgency, or incontinence. Elevated androgen levels can also affect bladder function, potentially leading to increased bladder sensitivity [2].

Other hormonal changes that can influence external urethral sphincter relaxation include progesterone deficiency. Progesterone is a cell-membrane stabilizer, and when in low levels, may lead to poor bladder sensation and detrusor underactivity, a staple of a condition known as Fowler's syndrome [26]. Hormonal imbalances can also lead to weak pelvic floor muscles. There is a significant correlation between luteinizing hormone (LH) levels and the pelvic organ prolapse symptoms in women with PCOS [27]. Obesity as well, which is a common comorbidity in women with PCOS, can contribute to an increase in intra-abdominal pressure, increasing the risk of pelvic floor dysfunction and urinary incontinence [17].

4. PCOS and urinary tract infections (UTIs)

Women with PCOS are more prone to infections, including UTIs. This is due to immune dysregulation associated with PCOS, in addition to insulin resistance and obesity that further impair the immune system and increase susceptibility to infections [28]. Hormonal and metabolic imbalances can also contribute to incomplete bladder emptying and urinary stasis which potentially predispose to UTIs [29].

Another factor that contributes to UTIs in women with PCOS is the alteration in vaginal pH in response to elevated androgen levels which makes the genital environment more suitable to infections, particularly ascending ones resulting in UTIs [29].

5. PCOS and bladder pain syndrome/interstitial cystitis

Chronic pelvic pain is a common condition in women with a major urogynecological component. It is defined as non-cyclic pain involving the pelvis, lower abdomen and back, medial thigh, or perineum that presents for more than 6 months. Women with PCOS may experience chronic pelvic pain due to several factors including ovarian cysts, irregular menstrual cycles, endometriosis, chronic inflammation, pelvic floor dysfunction, and bladder pain syndrome [1].

Bladder pain syndrome/interstitial cystitis (BPS/IC) is defined as chronic pelvic or supra-pubic pain that affects the urinary bladder with symptoms of urinary frequency, urgency, and nocturia. This condition is characterized by chronic inflammation of the inner bladder wall [30]. Bladder pain syndrome and PCOS share common inflammatory pathways making both conditions somehow associated, with particular similar symptomatology. The inflammatory pathways linking PCOS and bladder hypersensitivity, a subtype of BPS/IC, are complex, involving shared cytokines, oxidative stress, and hormonal imbalances, and the chronic low-grade inflammation seen in PCOS may predispose individuals to bladder hypersensitivity or exacerbate preexisting bladder conditions:

1. Common inflammatory mediators:

    - Cytokines: Both conditions show increased cytokine production, particularly tissue necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interleukin 1-beta (IL-1β), contributing to inflammation and tissue remodeling. In PCOS, these cytokines exacerbate insulin resistance and ovarian dysfunction, while in bladder hypersensitivity, they are involved in bladder tissue inflammation and hyperalgesia [31, 32].

- Oxidative stress: Both PCOS and bladder hypersensitivity are associated with increased oxidative stress, which can damage cells and tissues. In PCOS, oxidative stress can affect the ovaries and endometrium, while in bladder hypersensitivity, it contributes to bladder wall inflammation and dysfunction [32, 33].

2. Hormonal imbalance:

- In PCOS, hormonal imbalances particularly elevated androgens contribute to a sustained inflammatory state. These elevated androgens can also affect the urothelium and may increase the bladder's sensitivity [28].

3. Insulin resistance:

- Insulin resistance is another factor that connects PCOS and bladder hypersensitivity. Both conditions are commonly associated with insulin resistance, and insulin itself can be proinflammatory. Elevated insulin levels can affect inflammatory markers, which might exacerbate symptoms of both PCOS and bladder hypersensitivity [33].

Endometriosis is another common gynecologic condition where migrating endometrial tissue is present outside the uterine cavity resulting in chronic pelvic pain. Endometriosis is now understood more as a systemic disease, with the endometriosis tissue leading to an inflammatory response and causing a range of symptoms including pelvic pain, infertility, and bladder dysfunction [30]. Symptoms of PCOS, endometriosis, and bladder pain syndrome may overlap and coexist in the same patient. Bladder dysfunction in women with endometriosis is a result of a combination of direct mechanical effects from endometriotic lesions, inflammatory mediators, nerve involvement, pelvic floor dysfunction, and hormonal influences:

5.1 Direct infiltration of bladder tissue

5.1.1 Endometriotic lesions on the bladder

Endometriosis can directly affect the bladder by implanting on or around it. These lesions can cause irritation, fibrosis, and inflammation of the bladder wall, leading to urinary urgency, frequency, and dysuria. Deep pelvic endometriosis, which may involve the muscular layer of the bladder, can result in bladder contractility dysfunction and difficulty in fully emptying the bladder, contributing to urinary retention [34].

5.2 Neuropathic mechanisms

5.2.1 Nerve involvement

Endometriosis lesions may also affect the pelvic nerves that innervate the bladder. Direct irritation or inflammation of these nerves can contribute to bladder dysfunction, including pain and sensory changes related to urination (e.g., urgency or hesitancy). On the other hand, the surgical management of endometriosis may affect pelvic and bladder innervation and control the symptoms [35].

5.3 Pelvic adhesions

Adhesions formed as a result of endometriosis can cause organs in the pelvis, including the bladder, to adhere to each other. These adhesions can lead to chronic pelvic pain, dysuria, and incomplete bladder emptying.

The complexity of this interaction often requires a multidisciplinary approach to treatment, including pain management, pelvic floor therapy, and in some cases, surgical intervention.

6. PCOS and nephrolithiasis

Patients with PCOS have a 59% increased risk of developing nephrolithiasis compared to healthy women [36]. The majority of kidney stones are calcium stones, either calcium oxalate or calcium phosphate, followed by uric acid, cystine, struvite, and lastly miscellaneous stones. There are modifiable and nonmodifiable risk factors for kidney stones. Some modifiable risk factors can be divided into urinary, dietary, and pharmacological factors. Urinary factors include high urinary calcium, oxalate, and uric acid, as well as low urinary citrate and urine volume (< 1 L/day). Additionally, urine pH can predispose to the formation of certain stones. Formation of uric acid stones favors an acidic urinary environment, whereas the formation of struvite stones favors an alkaline urinary environment. Another modifiable risk factor is diet. Calcium stone formation is supported by a higher intake of oxalate, sodium, sucrose, fructose, vitamin C and a lower intake of water, calcium, potassium, and phytate. On the other hand, uric acid stones are precipitated by higher intakes of animal protein and lower intakes of fruits and vegetables [37]. Nonmodifiable risk factors of nephrolithiasis include gender, genetic susceptibility, family history, and certain medical conditions like diabetes mellitus, hypertension, and obesity.

Nephrolithiasis is evidently influenced by hyperandrogenism, a key player in the pathophysiology of polycystic ovarian syndrome. Testosterone mediates urinary oxalate excretion at the molecular level. It also stimulates the formation of glycolic acid oxidase, a hepatic enzyme, which is needed in the formation of urinary oxalate [38]. In a study by Li et al. [39], a group of patients known to have kidney stones underwent percutaneous nephrolithotomy and ultrasound guided kidney tissue biopsy. Immunohistochemistry results of the kidney tissue biopsies revealed upregulation of androgen receptors compared to normal kidney tissue biopsies [39]. Serum testosterone was also found to be elevated in male patients with urolithiasis compared to male controls [40]. In spite of the limited studies in PCOS-affected individuals, it can be inferred that hyperandrogenism can increase the risk of stone formation in PCOS-affected individuals by increasing urinary calcium oxalate levels [40].

Obesity and insulin resistance also predispose patients with PCOS to form kidney stones [36]. Studies have shown that women who weigh more than 100 kilograms have an increased risk of developing kidney stones by nearly 90% [41]. In addition, a positive correlation between increasing body weight index (BMI) and nephrolithiasis was deduced in a Bayesian meta-analysis by Rahman et al. [42]. They found individuals with higher BMIs have increased uric acid excretion and lower urinary pH, which aid in stone formation. Moreover, diabetes is significantly associated with nephrolithiasis through insulin resistance [42]. Normally, insulin has an inhibitory effect on ammoniogensis in the renal tubules. Insulin suppresses glutamine uptake

and metabolism, as well as enhances bicarbonate reabsorption. With insulin resistance, this effect is reduced, leading to increased ammoniogenesis and excretion of ammonia in urine [43]. This, in turn, lowers the urinary pH and creates an ideal environment for uric acid stone formation. Nonetheless, insulin resistance also promotes calcium stone formation by lowering urinary citrate levels and inducing hypercalciuria at the renal tubules [42].

Other PCOS-associated metabolic comorbidities, such as hypertension and dyslipidemia, similarly contribute to the added risk of nephrolithiasis in PCOS. The meta-analysis by Rahman et al. [42] documented statistically significant relationships between nephrolithiasis and both hypertension and dyslipidemia. Hypertensive patients are observed to have higher urinary levels of calcium and oxalate, as well as lower urinary levels of citrate. Moreover, a 1.586-fold increased risk of nephrolithiasis is seen in patients with dyslipidemia. The underlying pathophysiology is presumed to be oxidative stress. It contributes to stone formation by increasing urinary calcium, phosphate, or oxalate and lowering urinary citrate or magnesium [42]. To summarize, PCOS-affected individuals are at an increased risk of developing nephrolithiasis. This can be attributed to altered urinary solutes and pH levels, which are evidently influenced by hyperandrogenism and metabolic comorbidities associated with polycystic ovarian syndrome.

7. PCOS and kidney disease

Correlation between PCOS and renal injury is subjective to academic curiosity. PCOS is a proinflammatory state with raised inflammatory markers including C-reactive protein and uric acid. In a meta-analysis assessing the relationship between PCOS, hyperuricemia, and renal impairment, PCOS-affected women were shown to have significantly elevated uric acid levels compared to controls. This may be attributed to the effects of testosterone on uric acid reabsorption in the renal tubules [44]. Hyperuricemia is a risk factor for kidney disease [45]. Its effects on the kidney were summarized in a study by Gozukara et al. [42]. It harms the kidney by promoting oxidative stress, renin-angiotensin system activation, and glomerular hyperfiltration [46].

Hyperandrogenemia induces oxidative stress and possibly contributes to renal impairment in PCOS. This was demonstrated using animal models of PCOS. Data from different studies showed that female hyperandrogenic rats had elevated glomerular filtration rates (GFR), proteinuria, serum creatinine levels, cystatin C, and serum blood urea nitrogen levels [16, 36]. Testosterone also activates a pro-apoptotic pathway which leads to mitochondrial disruption and renal cell death [16]. Song and colleagues studied urine samples of PCOS-affected patients and found higher amounts of renal tubular injury markers compared to controls [47]. Furthermore, a positive correlation was captured between hyperandrogenemia and renal tubular cell injury [16, 47].

PCOS-associated metabolic comorbidities are also well-established risk factors for kidney disease [45]. Approximately 70% of type 2 diabetics show glomerular hyperfiltration. Growth hormone and insulin growth factor 1 (IGF-1) enhance renal blood flow. This allows for an abnormal increase in the filtration of solutes through the glomerulus, ultimately resulting in oxidative stress and renal dysfunction [44, 46]. Hypertension is also prevalent in PCOS-affected patients as it is partially modulated by the effects of hyperandrogenism [16, 46]. It leads to nephron loss by increasing glomerular pressure and damaging the renal endothelium [48].

Further research is warranted to fully understand the relationship between polycystic ovarian syndrome and renal disease. Current literature describes the proinflammatory effects of hyperandrogenism. It promotes excessive reabsorption of uric acid in the kidneys, leading to oxidative stress. Testosterone also mediates the pathway responsible for renal cell apoptosis. Moreover, PCOS is associated with metabolic disorders, including diabetes mellitus and hypertension, which predispose PCOS-affected patients to kidney disease through glomerular hyperfiltration and endothelial damage, respectively. In essence, inflammation, hyperuricemia, hyperandrogenemia, and PCOS-associated metabolic syndromes predispose PCOS-affected patients to renal impairment [16, 44–48].

8. PCOS and Fowler's syndrome: A unique association

In young women, urinary retention is a relatively rare clinical problem, which often goes underdiagnosed. Fowler's syndrome (FS) is a non-neurological, often painless, urinary retention disorder that is linked to impaired urethral relaxation. According to Szymański et al. [13], Fowler's syndrome is characterized by a patient's large-sized bladder capacity, increased maximal urethral closure, reduced sensation, and detrusor underactivity [13]. Since the first publication of FS in 1988, researchers have attempted to learn more about the disorder, and not all patients exhibit the typical presentation of the condition. Trachta et al. [49] followed the case of a previously healthy 14-year-old girl who complained of gradual loss of frequency of the need to urinate to twice per day and protracted hesitancy. Additionally, her urinary stream has become weak and slow at the beginning before being interrupted. Her straining did not produce a stronger stream. Upon diagnosis, physicians found that she was suffering from FS. Using Trachta, Watcher, and Kriz's case, FS is characterized by difficulty in urinating, often with a feeling of being unable to empty the bladder completely. Patients with FS lack the usual urge to urinate [49].

8.1 Pathophysiology

FS is associated with an abnormal bladder sphincter electromyography (EMG), a component of urodynamic assessments found during the diagnostic tests for patients presenting with such conditions, and in FS it usually shows complex, repetitive discharges and decelerating bursts. This suggests an issue with the sphincter's capability to relax, which leads to urine retention. Based on the initial study carried out in 1988, C. J. Fowler and other experts found that the majority of the women they studied who had developed urinary retention they studied exhibited abnormal EMG activity [12]. The EMG abnormalities suggest that the urinary sphincter does not relax sufficiently resulting in blockage of urine flow and thus urinary retention. It is believed that an involuntary contraction of the sphincter prevents it from relaxing, leading to high urethral pressure and impaired voiding.

Another possibly related cause of the urinary retention that FS patients exhibit is a degree of detrusor underactivity (DU). DU is usually characterized by increased voiding time and occasionally a sensation of or actual incomplete emptying of the bladder, usually also coupled with urinary hesitancy, reduced sensation on filling, and slow urinary stream. In FS, chronic retention of urine can result in secondary detrusor underactivity due to overdistension and neural inhibition. Therefore, detrusor underactivity is a secondary effect of FS [50].

8.2 Hormonal influences

Several hypotheses have emerged that attempt to explain the cause of urethral sphincter dysfunction in FS, and one such hypothesis involves suspected hormonal changes due to the association of FS with polycystic ovary syndrome (PCOS). Hormonal changes cause abnormal stabilization of the sphincteric muscle membrane, failure of the striated muscle of the urethral sphincter to relax, and prevention of the bladder afferent signals from reaching the brain resulting in neurogenic dysfunction [13].

8.3 Diagnosis and management considerations

The diagnosis process for women with Fowler's syndrome requires eliciting the characteristic history of the inability to pass urine for 24 hours or longer. For younger women, other characteristic symptoms to consider include the lack of the urge to urinate even though the bladder is causing increasing pain or discomfort in the abdomen. Additional tests are required to evaluate the bladder function and exclude other causes. One conventional approach is the sphincter electromyography (EMG) where a fine electrode measures and records the activity of the small urethra sphincter. Dr. Fowler, through her experience with young women experiencing painless urinary retention and no clear anatomic or neurological cause, hypothesized that external urethral sphincter could be involved. To test her hypothesis, she used concentric needle EMG to record electric activity and proved that ephaptic inter-muscle fibers signal transmission leads to massive waves of activity known as complex repetitive discharges. Striated muscle fibers of the external urethral sphincter activate one another through adjacent membranes in parallel waves and not through normal synaptic transmission [12].

The main limitation with the EMG approach is that it is invasive, and therefore, there was the need to come up with a less invasive and accurate method. This led to the utilization of the urodynamics test, which involves noninvasive uroflowmetry, followed by invasive cystometry and a pressure flow study, either EMG or video assisted, or neither. Video urodynamics uses standard urodynamics assessments but coupled with fluoroscopic imaging with radiographic contrast in the bladder. This approach is considered more informative in neurological patients who have neurogenic bladders, as well as patients have had prior surgery or trauma-related anatomical defects [51].

When it comes to the treatment and management of FS in women with PCOS, treatment aims to ensure the emptying of the bladder. On top of hormonal and nutritional management of PCOS, targeted urological interventions are essential including clean intermittent self-catheterization (CIC), medications such as alpha-blockers, and sacral neuromodulation (SNM). One limitation of CIC is that patients may have a challenge tolerating the frequent macroscopic hematuria and pain associated with the process, particularly in FS patients [49]. In a 2005 study by Mostafa Elhilali and two other physicians, out of 9 patients with chronic urine retention who underwent SNM treatment, 7 showed significant improvement [52]. In other words, 78% of the sample population showed significant improvement in restoring voiding through SNM.

9. Clinical implications and management strategies

Given the heterogeneity of the symptoms of PCOS and the constant evolution of the condition, experts agree on taking a multidisciplinary approach in the management of the condition. According to Wolf et al., a multidisciplinary approach to PCOS

is believed to be an effective strategy that will enable the coordination of care and provide a chance to innovate and research across the full spectrum of PCOS [53]. Gynecologists diagnose PCOS through assessing the menstrual history of the patient, conduct physical exams, order blood tests, and conduct ultrasound tests to evaluate hyperandrogenism. Being an endocrinological disorder, an endocrinologist's involvement in the evaluation of PCOS is also essential. PCOS is also associated with increasing urological conditions, warranting the need for a urologist. For instance, a strong and positive relationship exists between PCOS and chronic urinary retention in young women [3]. Women with PCOS also experiences issues with overactive bladder (OAB), high prevalence to urinary tract infections due to hormonal imbalance, and chronic pelvic pain. Therefore, in managing urinary conditions for women with PCOS, the expertise of a urologists plays a key role in managing the urinary-related symptoms.

Recently, two multidisciplinary treatment facilities managing PCOS have published their successful experiences. The American Family Children's Hospital in Wisconsin, established in 2005, comprises a pediatric endocrinologist, a reproductive endocrinologist, and endocrine nurse, health psychologist, dietitian, and a pediatric gynecologist. A study to evaluate the effectiveness of the clinic's management of PCOS showed great success, especially through metrics such as high patient ratings of satisfaction with the treatment criteria and the clinic's retention of patients, who diligently come back. The second clinic is in the Royal Berkshire Hospital in Reading, Berkshire, United Kingdom. Similar to the evaluation applied to the American Family Children's Hospital, most patients were satisfied with the outcome of the multidisciplinary action taken by the clinic [53]. Both these cases reveal how effective a multidisciplinary approach to treating and managing PCOS is.

9.1 Lifestyle interventions

There is a high prevalence of obesity among women with PCOS, estimated to range between 30 and 70%. Obesity is likely to result in oxidative stress in the urethral mucosa, loss of urethral elasticity, and reduction in the amount of collagen. Eventually, an increase in the inter-abdominal pressure results in lower urinary system symptoms [3]. As a result, the management of patients' weight and diet contribute significantly to minimizing and managing the urological impacts of PCOS. In a review by Moran, et al., the researchers concluded that weight reduction could result in clinical benefits for those with PCOS [54]. Women with urological concerns such as UTIs, Fowler's syndrome, and urinary tract dysfunction ought to focus on managing their weight and improving insulin sensitivity while considering lifestyle and dietary practices that might have a positive impact on their health overall. For instance, choices of foods such as those with low glycemic index, which would help regulate blood sugar levels, and healthy fats, including omega-3 fatty acids, would greatly impact their symptomatology [55].

9.2 Pharmacological and surgical management options for urological manifestation

Young women with PCOS have an increased risk of nephrolithiasis. Dietary modifications and lifestyle changes are usually the first line of management. Medication and surgery are also viable options. Based on the stone composition, different medications may be prescribed. For cystine stones, penicillamine and potassium citrate are

administered. For uric acid stones, drugs such as allopurinol and potassium citrate are given to patients with kidney stones [52].

Sacral neuromodulation (SNM) is an effective management strategy used for patients suffering from dysfunctional urinary retention. SNM is a minimally invasive procedure that has a high success rate in managing FS among women with PCOS [52]. Thirdly, for women suffering from urinary conditions such as dysfunctional urinary retention and alpha-blockers such as doxazosin, which relax the muscles of the bladder and the bladder neck, may ease difficulties with urine flow [56]. Lastly, for the management of UTIs, prophylactic antibiotics are used to help patients manage their infections.

9.3 Importance of early detection and patient-centered care

PCOS is one of the most common hormonal disorders among women of reproductive age, yet it often goes undiagnosed or misdiagnosed for years. Early detection of PCOS is critical. Early detection is not just for managing symptoms, but for preventing long-term complications and urological associations. Identifying PCOS early allows for timely interventions, including lifestyle modifications, targeted medications, and regular monitoring of associated health risks. It also enables patients to make informed decisions about their reproductive health and overall well-being.

10. Research gaps, future directions, and summary

The association between PCOS and urological symptoms has been investigated for decades. However, considerable deficiency in our literature exists. This creates valuable opportunities for further research. Addressing them is imperative in advancing our collective knowledge and providing both effective and patient-targeted approaches to care. Examples of research deficiencies include gaps in theoretical perspectives, methodological strategies, and clinical practice.

Extensive theoretical frameworks have been proposed with regards to the pathophysiological mechanisms linking PCOS and urological disorders, including lower urinary tract symptoms, urinary tract infections, nephrolithiasis, and bladder pain syndrome. Researchers continue to debate the underlying factors responsible for mediating these urological manifestations in PCOS patients. While some studies attribute hyperandrogenism as the key player, others have provided statistically significant evidence supporting the role of insulin resistance. In addition, chronic inflammation and oxidative stress have been proposed as contributing factors. The underlying etiological processes influencing the aforementioned factors involve genetics and epigenetics as well as environmental factors, which further expand on the multifaceted nature of this clinical dilemma.

The methodological strategies employed in exploring the relationship between urological symptoms and PCOS may be deficient due to small sample sizes, as well as a lack of long-term studies and standardized diagnostic tools. Recruiting large populations for research purposes is a difficult task, resulting in most studies relying on small sample sizes. This has restricted our understanding of urological symptoms in different PCOS subtypes. Additionally, cohort studies and randomized control trials are challenging to conduct considering ethical restrictions. Consequently, many studies were conducted using animal models. Furthermore, the absence of standardized diagnostic tools warrants variability in results. They are necessary in providing a uniform foundation and reducing confounding effects.

Shortcomings in clinical practice contribute to unaddressed research questions. Although PCOS is recognized for its metabolic, reproductive, and endocrine manifestations, its urological symptoms are overlooked and underreported. Raising awareness about urological manifestations in PCOS is a start to narrowing the research gap in addition to targeting its management and enhancing patient quality of life. This can be further facilitated by incorporating PCOS-specific recommendations in urological guidelines. Moreover, the advancement of precision medicine allows us to cater individualized treatment based on the subtype of PCOS using novel therapeutic approaches, including neuromodulation and hormonal therapies.

In conclusion, polycystic ovarian syndrome (PCOS) is a complex and multifaceted condition that extends far beyond reproductive and metabolic domains. Its underrecognized impact on the genitourinary system is increasingly supported by emerging evidence linking hormonal imbalances, insulin resistance, chronic inflammation, and pelvic floor dysfunction to a variety of urological disorders. From lower urinary tract symptoms and recurrent UTIs to nephrolithiasis and bladder pain syndromes, women with PCOS are disproportionately affected by these conditions. Unique associations, such as with Fowler's syndrome, further emphasize the need for heightened clinical awareness and interdisciplinary management strategies that include urologists alongside gynecologists, endocrinologists, and other specialists.

As research continues to evolve, it is critical to bridge the existing gaps in both evidence and clinical practice. Early diagnosis of PCOS and its urological implications, combined with patient-centered care models, can help mitigate long-term complications and improve quality of life. Future directions should focus on developing standardized diagnostic tools, conducting larger-scale studies, and implementing PCOS-specific recommendations in urological guidelines. Ultimately, a multidisciplinary and individualized approach—supported by robust research—will be key in addressing the full spectrum of PCOS and ensuring holistic care for affected individuals.

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Section 3

The Diagnosis of Polycystic Ovary Syndrome

Chapter 5

AI-Driven Polygenic Risk Scores and Genetic Insights for Polycystic Ovary Syndrome (PCOS) Susceptibility and Diagnosis

Susmit Kosta and Megha Singh

Abstract

Polycystic ovary syndrome (PCOS) is a complex, multifactorial endocrine disorder influenced by both genetic and environmental factors. Recent advancements in artificial intelligence (AI) and polygenic risk scores (PRS) have revolutionized the understanding of genetic susceptibility and diagnosis of PCOS. PRS aggregates the effects of multiple genetic variants identified through genome-wide association studies (GWAS) to predict an individual's genetic predisposition to PCOS. AI-driven models enhance the accuracy and predictive power of PRS by integrating large-scale genetic data with clinical, hormonal, and metabolic profiles. Machine learning (ML) algorithms can identify hidden patterns, improve phenotype classification, and refine diagnostic criteria, contributing to early detection and personalized treatment strategies. This chapter explores the application of AI-driven PRS in PCOS, highlighting the genetic architecture, key genetic markers, and the role of bioinformatics in improving diagnostic accuracy and risk stratification. Leveraging AI and PRS holds promise for advancing precision medicine in PCOS management and improving patient outcomes.

Keywords: polycystic ovary syndrome (PCOS), polygenic risk score (PRS), artificial intelligence (AI), genome-wide association studies (GWAS), machine learning (ML), precision medicine

1. Introduction

1.1 Background and epidemiology of PCOS

Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic disorder affecting 8–20% of women of reproductive age, depending on diagnostic criteria [1–3]. First identified by Stein and Leventhal in 1935, PCOS is marked by hyperandrogenism, oligo/anovulation, menstrual irregularities, infertility, and polycystic ovarian morphology (PCOM). It is frequently associated with insulin resistance, obesity, dyslipidemia, and impaired glucose tolerance [2, 4].

Prevalence estimates vary: 4–8% using NIH 1990 criteria, 12–20% under Rotterdam 2003, and ~10% with AE-PCOS criteria [3–5]. These variations reflect the

syndrome's heterogeneity and complicate standardization in public health. Geographic and ethnic disparities also exist; populations from India, South Asia, and the Middle East report higher prevalence (9–22% in Indian studies), likely due to genetic predisposition and lifestyle factors such as urbanization, poor diet, and sedentary behavior [6, 7]. In contrast, East Asian populations may be underdiagnosed due to cultural and healthcare access barriers [8].

Beyond reproductive concerns, PCOS carries long-term metabolic risks, including a fourfold increase in type 2 diabetes, metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), cardiovascular disease, and endometrial hyperplasia [4, 9]. Mental health conditions such as anxiety and depression are also more frequent [10]. Delayed diagnosis, particularly in adolescents and perimenopausal women, is common, often taking over 2 years from symptom onset [2, 6].

Given its complex and multifactorial nature—genetic, hormonal, metabolic, and environmental PCOS is well-suited for precision medicine. Emerging tools such as artificial intelligence (AI) and polygenic risk scores (PRS) show promise in enhancing early detection, risk stratification, and individualized treatment approaches [3, 10].

This chapter explores how PRS, powered by AI, can enhance the prediction, diagnosis, and personalized management of PCOS. By integrating genetic, clinical, and metabolic data through advanced ML and bioinformatics pipelines, the chapter provides a framework for precision medicine in PCOS. It emphasizes the clinical utility of AI-enhanced PRS, highlights the limitations of traditional approaches, and presents future directions for equitable and effective care.

1.2 Clinical heterogeneity and diagnostic challenges

PCOS is a clinically heterogeneous disorder encompassing a broad spectrum of reproductive, endocrine, and metabolic features [1, 11]. Its presentation varies with age, ethnicity, body weight, and environmental influences, making diagnosis and treatment challenging [5]. Common clinical features include menstrual irregularities (oligo-/amenorrhea), hyperandrogenism (hirsutism, acne, alopecia), and PCOM on ultrasound [1, 12]. However, not all patients exhibit all features. Some present with cosmetic concerns, and others with infertility or metabolic issues. Symptoms may evolve over time, for example, menstrual issues often improve with age, while metabolic risk increases [3].

PCOS is currently diagnosed using three major criteria sets, as summarized below (**Table 1**):

The choice of criteria significantly impacts prevalence estimates, phenotype classification, and therapeutic responses [5, 13]. For instance, the "non-hyperandrogenic" phenotype has lower metabolic risk, raising questions about its inclusion in the PCOS spectrum [14].

Criteria set	Year	Required features	Notes
NIH	1990	Hyperandrogenism + oligo-/anovulation	Excludes other causes
Rotterdam	2003	Any 2 of: hyperandrogenism, oligo-/anovulation, PCOM	Widest diagnostic scope
AE-PCOS society	2006	Hyperandrogenism + ovarian dysfunction	Emphasizes androgen excess

Table 1.
Major diagnostic criteria for PCOS.

Heterogeneity also hampers research standardization, clinical trial reproducibility, and genetic studies requiring uniform phenotypes [13, 15]. Adolescents and lean women are often underdiagnosed due to symptom overlap with normal puberty or aging [16].

No single biomarker currently offers definitive diagnosis. While serum testosterone, AMH, and LH:FSH ratios are commonly measured, they lack consistent diagnostic reliability. PCOM criteria also vary based on ultrasound technology and methodology (follicle count vs. ovarian volume) [12, 17].

Emerging approaches using PRS and AI are promising for objective and scalable diagnosis. These tools can aid in identifying PCOS across diverse phenotypes, enabling personalized care and improved long-term outcomes [15, 17].

1.3 Genetic architecture of PCOS

PCOS has a complex, polygenic and multifactorial genetic basis, with heritability estimates as high as 70% [15, 18]. Unlike monogenic disorders, PCOS results from the cumulative effects of numerous common genetic variants with the modest effect sizes, alongside environmental, hormonal, and epigenetic influences [18, 19].

Early candidate gene studies targeting steroidogenesis, insulin signaling, and gonadotropin pathways yielded inconsistent findings due to small cohorts and ethnic variability [20]. Genome-Wide Association Studies (GWAS) have since enabled discovery of over 20 reproducible loci associated with PCOS across diverse populations, especially in Han Chinese and European cohorts (**Table 2**) [21, 22].

These loci implicate pathways such as androgen biosynthesis, gonadotropin regulation, insulin resistance, and energy metabolism, reflecting the pleiotropic nature of PCOS-associated genes [19, 20, 23]. Many variants are also linked to traits like body mass index (BML) and metabolic syndrome [21, 23]. Despite these advances, individual single-nucleotide polymorphisms (SNPs) contribute only modestly (OR < 1.2), explaining a limited portion of total heritability often termed "missing heritability" [20, 24]. Explanations include rare variants with stronger effects, gene-gene and gene-environment interactions, and regulatory non-coding regions. To address this, whole exome sequencing, whole genome sequencing, and multi-omics approaches (transcriptomics, epigenomics, metabolomics) are now employed to uncover novel genetic contributors [22, 25].

Understanding PCOS's genetic architecture is crucial for building PRS and developing personalized management strategies that align with precision medicine goals [3, 10].

Gene/locus	Function	Contribution to PCOS pathophysiology
DENND1A (9q33.3)	Endosomal trafficking	Enhances androgen biosynthesis [21]
LHCGR (2p16.3)	LH/CG receptor	Affects ovulation, follicular maturation [22]
THADA (2p21)	Energy metabolism	Links PCOS with obesity and T2DM [23]
FSHB (11p14.1)	FSH subunit	Implicates gonadotropin imbalance [24]
HMGA2 (12q13.2)	Growth regulation	Correlates with early menarche, ovarian volume [22]

Table 2.
Key PCOS-associated genetic loci identified by GWAS.

Feature	Benefit
Integration of genomic + clinical data	Improves prediction accuracy [28]
Phenotypic clustering (phenomapping)	Identifies PCOS subtypes [29]
EHR integration	Enables real-time risk flagging [30]
Explainable AI (XAI)	Enhances model transparency and clinician trust [31]

Table 3.
Advantages of AI-enhanced PRS in PCOS.

1.4 Emerging role of AI and PRS in precision medicine

The integration of AI and PRS into PCOS management is reshaping the future of precision medicine in women's health [26, 27]. Traditional diagnosis relies on clinical phenotypes, which often fail to capture the disorder's biological complexity and variability [3]. PRS estimate a person's genetic susceptibility to PCOS by aggregating the effect of multiple SNPs from GWAS data [19].

However, standalone PRS lack context from clinical, hormonal, and lifestyle data. AI technologies, particularly machine learning (ML) and deep learning (DL), enhance PRS by integrating multi-dimensional datasets genomic, phenotypic, metabolic, and imaging to improve accuracy and personalize care (**Table 3**) [28, 29].

AI-enabled phenomapping classifies PCOS into subtypes (e.g., hyperandrogenic, lean, obese) and aligns treatment more precisely with patient profiles [29]. Embedding AI-PRS models in electronic health records (EHRs) allows early identification of high-risk individuals and prompts targeted testing or specialist referral [30].

Furthermore, Explainable AI (XAI) tools like SHAP and LIME enhance interpretability by showing which inputs (e.g., SNPs, AMH, BML) contribute most to a patient's risk score [31, 32]. This helps clinicians make transparent and personalized decisions. AI-enhanced PRS offers a proactive and data-driven approach to PCOS care supporting early detection, risk stratification, and tailored interventions. As datasets grow globally, these tools will become more inclusive, scalable, and transformative for reproductive endocrinology [31].

2. Genetic basis of PCOS

2.1 Heritability and familial patterns

PCOS demonstrates a strong genetic predisposition, with heritability estimates ranging from 60% to 70%, based on family-based and twin studies [25, 32]. First-degree female relatives of PCOS patients often display similar features such as hyperandrogenism, menstrual irregularities, and metabolic disturbances supporting a familial aggregation model [33, 34].

Importantly, daughters and sisters of affected women are up to five times more likely to develop the PCOS [35]. Even male relatives may exhibit traits such as insulin resistance and dyslipidemia, suggesting that the genetic basis transcends female-specific reproductive phenotypes [15].

Twin studies bolster this understanding, showing higher concordance of PCOS in monozygotic twins (who share 100% of their genome) compared to dizygotic twins (who share ~50%) [32]. This reinforces the polygenic nature of the disorder.

However, gene expression is modulated by environmental and epigenetic factors. Influences such as diet, physical inactivity, prenatal androgen exposure, and endocrine-disrupting chemicals may determine whether an individual with genetic susceptibility will manifest PCOS [36, 37]. Epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNAs may also mediate transgenerational inheritance, especially through in-utero programming in daughters of PCOS mothers [38]. Familial and epigenetic evidence supports the use of genome-wide sequencing to identify at-risk individuals and understand the biological basis of PCOS.

2.2 Key genetic loci identified through GWAS

The development of GWAS has significantly advanced the understanding of PCOS genetics. Unlike candidate gene studies, GWAS survey the entire genome in an unbiased manner, identifying SNPs associated with the disease risk [21].

To date, over 20 PCOS-associated loci have been identified, initially in Han Chinese populations and later validated in European and multi-ethnic cohorts. These loci fall into three major functional categories: reproductive regulation, metabolic control, and developmental processes (**Table 4**) [28].

Although each SNP confers a small effect size (odds ratio $\sim$ 1.1–1.2), their collective influence forms the basis of PRS, allowing stratification of genetic susceptibility [19]. These loci also show pleiotropy, being associated with traits such as BML, type 2 diabetes, and age at menarche, indicating shared pathways between reproductive and metabolic disorders [39–43]. Future research using multi-omics and functional validation is needed to refine these associations and discover novel risk loci, especially in underrepresented populations.

2.3 Gene pathways involved in hormonal and metabolic regulation

PCOS arises from dysregulation of interconnected genetic pathways involved in reproductive and metabolic functions. Key processes include gonadotropin signaling, androgen biosynthesis, and insulin signaling (**Table 5**).

PCOS is a multifactorial disorder influenced by complex genetic interactions across several biological pathways. Variants in genes such as *LHCGR* and *FSHB* disrupt gonadotropin signaling, impairing the hypothalamic-pituitary-ovarian (HPO) axis and leading to abnormal luteinizing hormone (LH) to follicle-stimulating hormone

Gene/locus	Function	PCOS relevance
DENND1A	Endosomal trafficking	Upregulates androgen synthesis in theca cells
LHCGR	LH/CG receptor signaling	Affects ovulation and follicular development
THADA	Apoptosis and energy homeostasis	Related to type 2 diabetes and metabolic phenotype
FSHB	FSH beta-subunit	Alters follicular maturation and menstrual regulation
HMGA2	Growth factor regulation	Linked to early menarche and ovarian morphology
INSR	Insulin receptor signaling	Impairs insulin sensitivity
YAP1	Cell proliferation and apoptosis	Affects folliculogenesis and metabolism

Table 4.
Notable PCOS-associated genes and functions.

Pathway	Key genes	Role in PCOS
Gonadotropin signaling	LHCGR, FSHB	Disrupts LH/FSH balance; impairs ovulation and follicular development
Androgen biosynthesis	DENND1A, CYP11A1, CYP17A1, HSD17B5	Enhances steroidogenesis; causes hyperandrogenism and related symptoms
Insulin signaling	INSR, THADA, FTO	Reduces insulin sensitivity; promotes hyperinsulinemia and worsens androgen excess

Table 5.
Gene pathways implicated in PCOS.

(FSH) ratios. This hormonal imbalance interferes with proper follicular maturation and contributes to anovulation [21]. In the androgen biosynthesis pathway, the overexpression of *DENND1A.V2* in theca cells significantly enhances androgen production, while genes such as *CYP11A1* and *CYP17A1* further promote steroidogenesis, resulting in clinical manifestations such as acne, hirsutism, and infertility [24]. Insulin signaling and metabolic regulation also play a crucial role, with genes such as *INSR* and *THADA* modulating insulin sensitivity. Insulin resistance, present in approximately 50–70% of PCOS patients, exacerbates hyperandrogenism by stimulating androgen synthesis and reducing sex hormone-binding globulin (SHBG) levels, thereby increasing the concentration of free androgens [19]. Additionally, emerging evidence implicates genes such as *HMGA2* and *YAP1* in influencing ovarian morphology and follicular persistence, suggesting a developmental and structural component to PCOS pathogenesis [39]. The interplay among these pathways highlights the syndrome's clinical heterogeneity and reinforces the importance of adopting personalized, mechanism-targeted treatment strategies for effective management.

2.4 Limitations of traditional genetic studies

Despite significant progress, traditional genetic approaches have notable limitations in explaining PCOS's complex etiology (**Table 6**).

Candidate gene studies initially identified potential contributors to PCOS such as *CYP11A1* and *FSHR*; however, these findings were often irreproducible due to limited sample sizes and biased candidate selection. GWAS expanded the genetic landscape by identifying numerous loci associated with PCOS, but these common variants explain only a fraction of the disorder's heritability. Rare variants, as well as complex gene-gene and gene-environment interactions, remain largely undetected. Moreover,

Limitation type	Key issues
Candidate gene studies	Small samples, replication failures, assumption bias
GWAS	Identifies common variants only, low effect sizes, missing heritability
Ethnic and population bias	Overrepresentation of Europeans; poor generalizability to other populations
Environmental data exclusion	No integration with lifestyle, hormonal, or environmental variables
Translational gaps	Limited clinical implementation and functional validation

Table 6.
Limitations of traditional genetic studies in PCOS.

the majority of GWAS data are derived from European and East Asian populations, resulting in PRS that show the reduced predictive accuracy in South Asian, African, and Latinx cohorts. This population bias limits the generalizability of genetic risk assessments. Another critical shortcoming is the lack of multidimensional integration; genomic analyses often fail to incorporate the key environmental and physiological factors such as diet, physical activity, menstrual cycle patterns, and hormonal profiles, all of which significantly influence PCOS manifestation and progression. These gaps contribute to the limited clinical translation of genetic findings, as no single genetic marker or set of variants currently provides sufficient predictive power to warrant routine clinical testing for PCOS. The absence of validated biomarkers further hinders implementation into practice. These limitations underscore the necessity for a paradigm shift toward whole-genome sequencing, multi-omics integration, and artificial intelligence-driven predictive modeling, which together hold promise for a more comprehensive and accurate understanding of the genetic and phenotypic complexity underlying PCOS.

3. Polygenic risk scores (PRS) in PCOS

3.1 Concept and construction of PRS

PRS estimate an individual's genetic susceptibility to complex diseases such as PCOS by aggregating the effects of numerous SNPs. Unlike Mendelian disorders governed by a single gene, PCOS arises from the cumulative impact of many common variants, each exerting the modest effect size.

The construction of a PRS begins with conducting GWAS to identify SNPs significantly associated with PCOS. Each identified SNP is then assigned an effect size, such as an odds ratio or beta coefficient, which quantifies its contribution to disease risk based on GWAS summary statistics. An individual's PRS is calculated by summing the number of risk alleles they carry at each locus, weighted by the corresponding effect sizes. This cumulative score represents the individual's genetic predisposition to PCOS and can be used to stratify risk across a population. However, the predictive utility of PRS is influenced by several factors including the selection of SNPs, population ancestry, and the statistical models used, necessitating careful validation and calibration across diverse cohorts for clinical applicability.

Mathematically, the PRS for an individual iii is calculated as:

$$PRS_i = \sum_{j=1}^{n} \beta_j \cdot G_{ij} \tag{1}$$

Where βj is the effect size of SNP j, and Gij is the genotype dosage (0, 1, or 2) of the risk allele for individual i. Various methods exist to select and weight the SNPs used in the PRS. Simple thresholding methods use a fixed p-value cutoff (e.g., $p < 5 \times 10^{-8}$), while more sophisticated algorithms such as LDpred, PRSice, and BayesR account for linkage disequilibrium (LD) between SNPs, improving predictive accuracy by adjusting for genetic correlations. Multiple tools aid PRS calculation, including PLINK, PRSice, LDpred, and BayesR, which account for linkage disequilibrium (LD) to improve accuracy (**Figure 1** and **Table 7**) [35, 44–45].

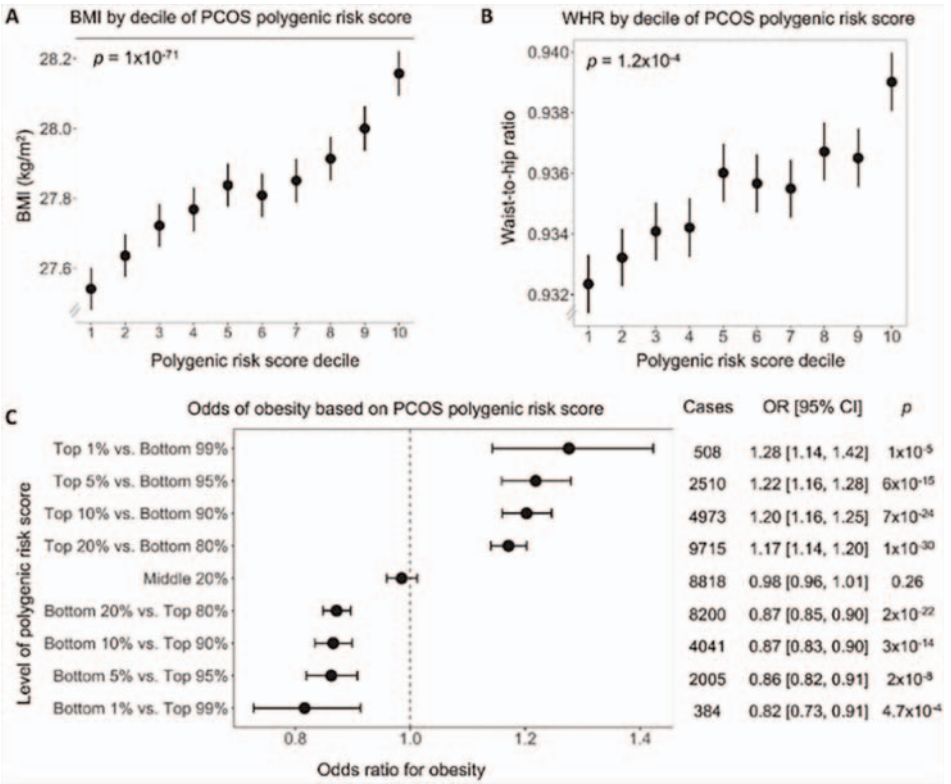

Figure 1.
Impact of PCOS polygenic risk score (PRS) on obesity metrics. (A) BML increases progressively across PRS deciles ($p = 1 \times 10^{-71}$). (B) Waist-to-hip ratio (WHR) shows a significant positive association with PRS decile ($p = 1.2 \times 10^{-4}$). (C) Odds ratios (ORs) for obesity vary significantly across PRS strata, with the top 1% showing the highest obesity risk (OR 1.28; $p = 1 \times 10^{-5}$), and the bottom 1% demonstrating protective association.

Factor	Impact
Number of SNPs included	Improves sensitivity but can reduce specificity
Sample size of GWAS	Larger studies improve effect size estimates
Ancestry match	Mismatched populations reduce accuracy
Quality control and imputation	Poor data quality skews scores

Table 7.
Key factors influencing PRS performance.

3.2 PRS in predicting PCOS susceptibility

PRS can stratify individuals by genetic risk prior to clinical symptom onset. Women in the top PRS decile have up to a fivefold higher likelihood of developing PCOS compared to those in the lowest decile [19, 27]. High PRS correlates with more severe hyperandrogenism, increased anovulation, and higher insulin resistance and obesity risk.

Moreover, PRS assists in distinguishing PCOS from conditions with overlapping symptoms such as congenital adrenal hyperplasia or hypothalamic amenorrhea. AI-

Application	Benefit
Risk prediction in asymptomatic women	Early lifestyle and metabolic interventions
Differentiation from related disorders	Reduces misclassification and guides therapy
Family screening	Proactive monitoring of daughters/sisters

Table 8.
Clinical utility of PRS in PCOS.

integrated PRS can improve diagnostic specificity by incorporating clinical and biochemical data (**Table 8**) [45].

3.3 Ethnic and population-level variability in PRS

PRS portability across ethnicities is limited. SNPs identified in European populations may not be informative in South Asians, Africans, or East Asians due to differences in allele frequencies and LD patterns [46].

South Asian women often show higher metabolic burden even at lower BML. Applying Euro-centric PRS models to such groups reduces predictive power and may exacerbate health disparities [47]. Strategies to improve PRS equity include conducting multi-ancestry GWAS (e.g., GenomeAsia 100K, All of Us), developing ancestry-specific LD panels, applying fine-mapping approaches, and using AI tools to adjust for population structure (**Figure 2**).

3.4 Clinical utility and challenges of PRS models

While PRS offer promising avenues for enhancing the clinical management of PCOS, several challenges impede their widespread application. In terms of utility, PRS could facilitate early identification of individuals at risk, enabling timely implementation of preventive strategies. They may also aid in subphenotype classification, distinguishing between hyperandrogenic and ovulatory forms of PCOS, and support personalized therapeutic planning, such as guiding the choice between metformin and

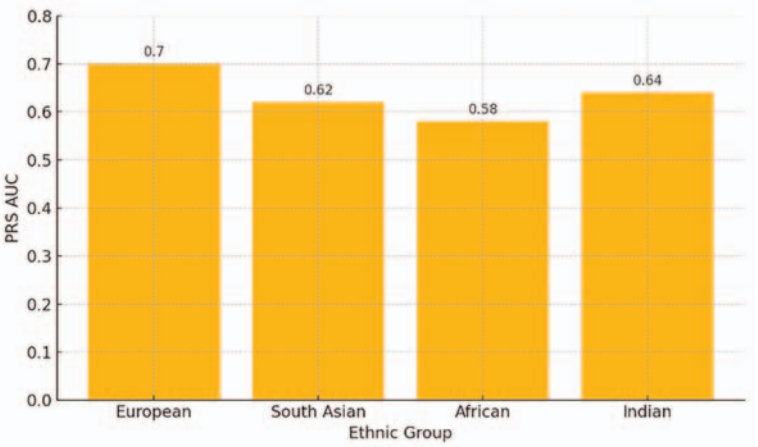

Figure 2.
Impact of ethnic diversity on PRS accuracy.

Category	Advantages	Challenges
Prediction	Early risk identification	Moderate AUC; poor generalizability
Diagnosis	Improves differential diagnosis	Complexity in clinical interpretation
Implementation	Scalable with EHRs and AI integration	Requires infrastructure, genetic counseling, cost analysis

Future directions include integrating PRS with hormonal profiles, EHR data, and AI-driven decision support tools for the precision management of PCOS.

Table 9.
Advantages vs. challenges of PRS in PCOS.

letrozole based on genetic predisposition. However, these potential benefits are counterbalanced by the notable limitations. The predictive accuracy of current PRS remains moderate, with AUC values hovering around 0.65 [48], which limits their standalone diagnostic utility. Furthermore, the interpretation of PRS results can be complex, posing challenges for both patients and healthcare providers in terms of understanding and actionable insight. The lack of robust validation across diverse populations further restricts generalizability, particularly for individuals of non-European ancestry. Additionally, the use of genetic risk profiling raises ethical concerns, including issues of privacy, data security, and the potential for genetic discrimination. These challenges highlight the need for continued refinement of PRS models, improved population inclusivity in genetic research, and the development of clear clinical guidelines and ethical frameworks for implementation (**Table 9**).

4. Artificial intelligence integration with PRS

4.1 Overview of AI, ML, and DL in biomedical research

AI is transforming biomedical research by enabling the interpretation of complex, high-dimensional datasets [22]. Key AI domains include machine learning (ML): supervised/unsupervised learning for prediction, classification, and biomarker identification [49]. And deep learning (DL): Uses multi-layer neural networks for modeling nonlinear relationships, excels in handling omics, imaging, and time-series data [50].

In PCOS, traditional PRS often fail to capture nonlinear interactions among genetic, hormonal, and environmental factors. AI-based models can integrate multimodal data, stratify phenotypes, and personalize predictions (**Figure 3**) [19].

4.2 Enhancing PRS with AI algorithms

AI methods expand the predictive utility of PRS by capturing complex relationships and handling multimodal data. Key approaches include DL models such as Convolutional Neural Networks (CNNs) are applied to genomic data, while Recurrent Neural Networks (RNNs) analyze time-series features like menstrual cycles. AI also enables explainability through tools like SHAP and Layer-wise Relevance Propagation (LRP) (**Table 10**).

4.3 Feature selection and dimensionality reduction

To enhance the predictive performance of polygenic models in PCOS, advanced feature selection and dimensionality reduction techniques are increasingly employed.

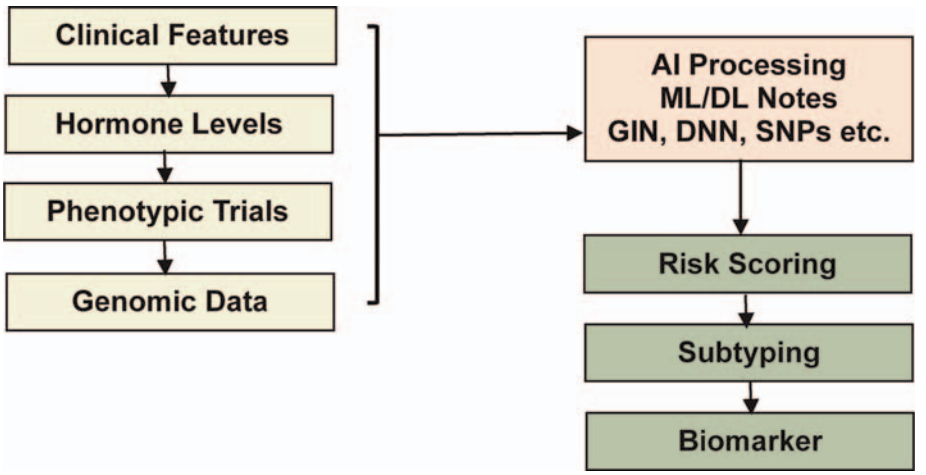

Figure 3.
AI applications in PRS for PCOS (ML/DL → risk scoring, subtyping, biomarker discovery).

Method	Advantages	Application in PCOS
Random forests (RF)	Handles SNP × phenotype interactions, ranks feature importance	Combine PRS with hormones, BMI, insulin resistance for stratified risk [51]
Gradient boosting (XGBoost/LightGBM)	High accuracy, robust to missing data	Used in complex multimodal prediction pipelines [31]
Neural networks (DNNs/CNNs/RNNs)	Learns patterns from raw data, integrates multi-omics	Used for phenotype prediction, menstrual pattern modeling [52]
SVMs	Effective with small datasets, high-dimensional SNP data	Classification of PCOS subtypes or comorbidities [53]
Clustering (K-means, GMM)	Identifies novel subtypes/endotypes	Phenomapping PCOS for precision interventions [54]

Table 10.
AI and machine learning methods for enhancing PRS in PCOS.

Feature selection methods help reduce noise and focus on the most informative SNPs. These include filter methods, such as correlation-based selection; wrapper methods like RFE; and embedded approaches, notably LASSO regression, which simultaneously perform variable selection and regularization to prevent overfitting [55]. In parallel, dimensionality reduction techniques offer powerful tools for managing the high-dimensional nature of genomic data. PCA is commonly used to correct for population stratification, ensuring that ancestry-related variations do not confound genetic associations. Techniques such as t-distributed stochastic neighbor embedding (t-SNE), and uniform manifold approximation and projection (UMAP) allow for the visualization of phenotypic clusters, facilitating subtype discovery within PCOS populations. Additionally, deep learning-based methods such as autoencoders can uncover latent data structures, capturing complex, non-linear relationships in genomic datasets that may otherwise remain undetected [56]. These computational strategies are critical for refining predictive models and moving closer to personalized risk assessment and management in PCOS.

4.4 Predictive modeling and validation

Predictive modeling integrates AI-enhanced PRS with clinical variables to forecast PCOS risk, subtypes, and therapy response (**Table 11**).

Model performance is evaluated on generalizability and calibration (e.g., Brier score). Few AI-enhanced PRS tools for PCOS have reached prospective validation, but ongoing research aims to achieve clinical translation (**Figure 4**).

4.5 Bioinformatics tools and pipelines

The integration of PRS and AI in PCOS research begins with meticulous data sourcing and preprocessing, particularly from GWAS and high-throughput genotyping platforms. The quality and integrity of this foundational data significantly influence the accuracy and robustness of downstream predictive models, including both PRS computation and ML applications [58, 59]. GWAS play a pivotal role by comparing genetic variants across large cohorts of affected and unaffected individuals to identify SNPs associated with PCOS.

Step	Tools/methods	Outcome
Modeling	Logistic regression, RF, DNN, SVM	PCOS diagnosis, phenotype classification
Evaluation metrics	Accuracy, sensitivity, specificity, AUC-ROC, F1	Model performance benchmarking
Validation	Internal (k-fold CV), external (new datasets), prospective (clinical use)	Generalizability and reliability of AI-PRS models [57]

Table 11.
Techniques for data preprocessing in PRS-AI models.

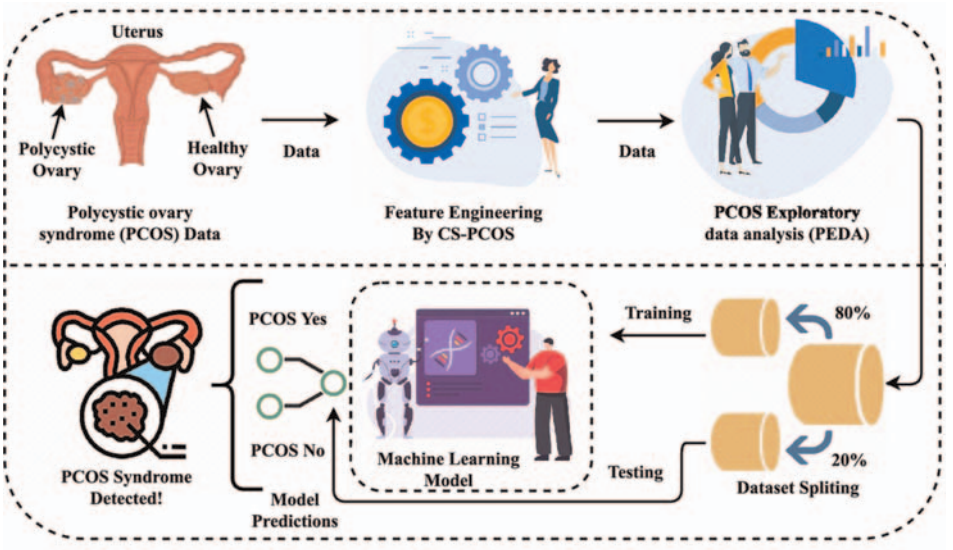

Figure 4.
The methodology of proposed AI-based predictive modeling and validation framework for PCOS. Source: Author's original work.

These studies typically yield critical information such as SNP identifiers, chromosomal locations, allele frequencies (risk and reference), effect sizes (e.g., odds ratios or beta coefficients), p-values, and confidence intervals. This data forms the backbone for constructing PRS and training AI algorithms to capture the complex genetic architectures. Leading consortia such as the UK Biobank, NHGRI-EBI GWAS Catalog, and FinnGen provide comprehensive, well-curated datasets that encompass PCOS-specific and related metabolic traits such as insulin resistance, obesity, and lipid abnormalities, thereby supporting integrative analysis and model generalizability [60].

4.6 Genotyping platforms and data types

Raw genetic data for PRS are obtained from genotyping arrays or sequencing. Common technologies include Illumina Infinium Arrays, Affymetrix GeneChips, and Whole-genome (WGS) or whole-exome sequencing (WES). These outputs are stored in variant call format (VCF) or PLINK binary files (BED/BIM/FAM) [37].

4.7 Preprocessing pipeline

Before applying PRS models or AI, multiple quality control (QC) steps are essential (**Table 12**).

4.8 Software for PRS construction (PLINK, PRSice, LDpred)

Accurate PRS generation requires software that handles large-scale genomic data, linkage disequilibrium (LD), and phenotype associations. The most widely used tools include PLINK, PRSice, and LDpred (**Table 13**).

Several computational tools have been developed to support the generation and refinement of PRS, each with varying capabilities in handling genomic complexities such as LD. PLINK remains a foundational tool widely used for basic PRS scoring, quality control, and genotype data preprocessing; however, it does not account for LD, which can limit its utility in highly polygenic traits like PCOS. PRSice extends these capabilities by introducing p-value thresholding and LD clumping, allowing for the removal of highly correlated SNPs and improving the specificity of selected variants. To further enhance predictive performance, LDpred employs Bayesian methods to explicitly model LD structures across the genome, thereby offering more accurate estimations of SNP effect sizes and increasing the overall predictive power of PRS for

Step	Description
Sample QC	Exclude individuals with high missingness, gender mismatch, outliers
Variant filtering	Remove SNPs with minor allele frequency (MAF) <0.01, HWE violation
Imputation	Use reference panels (e.g., 1000 Genomes, HRC) to infer missing genotypes
Population stratification	Control for ancestry using principal component analysis (PCA)
Phenotype harmonization	Standardize traits like BMI, hormone levels, menstrual cycle characteristics
Data integration	Link genetic, clinical, family history, and electronic health record (EHR) data

Tools such as PLINK, vcftools, and bcftools are widely used at this stage [61].

Table 12.
Preprocessing steps for PRS and AI modeling in PCOS genomic studies.

Tool	Primary function	Strength in PCOS research
PLINK	QC and base PRS scoring	SNP filtering, additive scoring, population control [58]
PRSice	Automated thresholding and LD clumping	Optimizes predictive power using p-value bins [37]
LDpred	Bayesian LD-aware scoring	Models complex genetic architectures with LD [62]

Table 13.
Comparison of PRS construction tools.

Framework	Key use	Application in PCOS genomics
TensorFlow	Large-scale, multimodal deep learning	PRS + hormones + imaging integration
scikit-learn	Classical ML, simple and efficient	Feature selection, clustering, baseline prediction
PyTorch	Flexible, time-series & transfer learning	Longitudinal data, variant annotation, deep models

Table 14.
Machine learning frameworks in AI-driven PRS for PCOS.

complex diseases such as PCOS [62, 63]. These tools form a critical computational pipeline for translating GWAS data into clinically meaningful risk assessments.

4.9 Machine learning frameworks (TensorFlow, scikit-learn, PyTorch)

AI integration into PRS allows for high-dimensional modeling of genetic and clinical features. Frameworks such as TensorFlow, scikit-learn, and PyTorch support deep learning and classical machine learning (ML) approaches in PCOS genomics (**Table 14**).

In the application of artificial intelligence to PCOS prediction and classification, several machine learning frameworks play pivotal roles depending on the complexity and scale of the task. TensorFlow is particularly suited for large-scale modeling tasks involving multimodal data integration, such as combining polygenic risk scores with hormonal profiles and imaging data like ultrasound scans. Its robust architecture supports deep neural networks and advanced computational graphs, making it ideal for complex, high-dimensional biomedical datasets [64]. For more conventional machine learning tasks, scikit-learn remains a popular choice due to its simplicity and efficiency in implementing algorithms such as logistic regression, random forests, clustering, and feature selection. It is widely employed for exploratory data analysis and rapid prototyping of predictive models [61]. PyTorch, on the other hand, offers flexibility through dynamic computational graphs and is well-suited for tasks involving time-series modeling and transfer learning. It also supports integration with genomic graph structures, enabling advanced applications in genomics and functional annotation of genetic variants [65]. These platforms collectively provide a versatile toolkit for developing AI-driven models that enhance the understanding and prediction of PCOS phenotypes.

4.10 Explainable AI (SHAP, LIME) for model interpretability

As PRS models grow in complexity, explainable AI (XAI) methods such as SHAP and LIME provide critical transparency.

Method	Core principle	Use in PCOS AI models
SHAP	Shapley values from cooperative game theory	Global and individual feature importance [31]
LIME	Local surrogate linear models	Case-wise explanation of model decisions [32]

Table 15.
Explainable AI methods for interpreting PRS-based PCOS models.

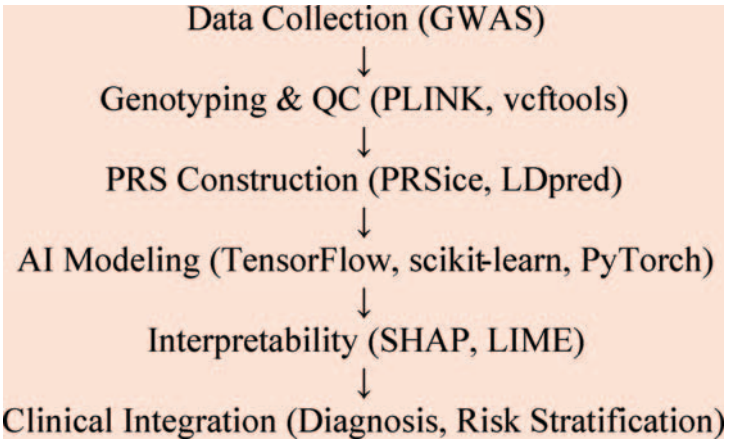

Figure 5.
Workflow of PRS-AI integration in PCOS.

4.11 Why interpretability matters?

AI-driven PRS models in PCOS include genetic, hormonal, and lifestyle data. Understanding which features influence predictions is essential for clinical adoption and regulatory compliance (**Table 15**) [31].

SHAP identifies consistent features (e.g., high PRS, elevated LH/FSH, BML >30) contributing to PCOS diagnosis. LIME approximates model behavior locally, aiding patient-specific interpretation (**Figure 5**).

5. Clinical implications and personalized medicine

5.1 Early risk prediction and diagnosis

Genetic risk stratification using PRS allows early detection of PCOS risk years before clinical manifestations appear. Pathophysiological changes begin during adolescence or even *in utero*, but conventional diagnosis is delayed due to reliance on symptoms like irregular menses or infertility [66].

5.2 Limitations of current diagnostic paradigms

Current criteria (NIH, Rotterdam, AE-PCOS) are symptom-based and often exclude adolescents or those with subclinical presentations, leading to diagnostic delays and prolonged metabolic dysfunction [3].

Approach	Current diagnostic (Rotterdam)	PRS-integrated early risk
Age of utility	Adulthood (≥18 years)	Adolescence or earlier (10–17 years)
Basis	Clinical symptoms	Genetic + hormonal risk
Key tools	Ultrasound, hormones	PRS + AI models + early labs
Outcome	Diagnosis after delay	Proactive screening and intervention

Table 16.
Genetic vs. traditional diagnostic approaches.

5.3 Integration with clinical indicators

When combined with early hormonal and phenotypic signs (e.g., elevated LH: FSH, early menarche, family history), PRS can flag high-risk individuals for early lifestyle intervention and hormonal monitoring (**Table 16**) [67].

5.4 Ethical considerations

Use of PRS in minors requires genetic counseling, informed consent, and privacy safeguards [68].

5.5 Phenotype subclassification and individualized profiles

PCOS is heterogeneous, and subclassification is critical for personalized care. Traditional phenotypes (A–D) based on Rotterdam criteria often obscure biologically distinct subgroups [69].

AI-enhanced subclassification: Unsupervised ML techniques (e.g., clustering, SVM) integrating PRS with hormones (AMH, LH, FSH), metabolic data, and clinical history enable data-driven subclassification aligned with the underlying biology (**Table 17**) [15].

5.6 Tailored interventions and therapeutic planning

With AI-enhanced PRS tools, therapies can be tailored to genetic risk and phenotypic subtype.

5.6.1 Therapeutic matching examples

- High-PRS + insulin resistance → Metformin, inositols
- Hyperandrogenism + DENND1A risk → OCPs, spironolactone
- Reproductive-only phenotype → Letrozole for ovulation induction

Feature	Rotterdam phenotypes	AI + PRS clusters
Input data	Clinical symptoms	PRS, hormones, metabolic and phenotype data
Granularity	Four main types	>6–8 data-driven clusters
Clinical use	Moderate	High for treatment planning

Table 17.
Rotterdam vs. AI-PRS subclassification.

Workflow stage	Tool/platform	Purpose
PRS calculation	PLINK, PRSice	Genetic risk scoring
Clinical decision support	SHAP, LIME	Explainable AI for risk interpretation
EHR integration	HL7/FHIR, SMART apps	Embedded risk alerts and care suggestions
Patient engagement	Education modules	Visual reports + genetic counseling

Table 18.
PRS clinical workflow components.

5.6.2 Lifestyle tailoring

Genetic profiles influence responsiveness to interventions such as low-GI diets, exercise regimens, or behavioral counseling.

5.7 Integrating PRS into clinical workflows

Embedding PRS and decision support tools into EHRs is crucial for clinical adoption (**Table 18**).

6. Challenges and future perspectives

6.1 Multi-ethnic representation and data diversity

Most PRS models are derived from European GWAS, limiting their predictive value in other populations (**Table 19**).

6.2 Ethical and social considerations of genetic risk prediction

As the clinical integration of PRS and AI-based genomic tools advances, several ethical and social concerns must be carefully addressed. One of the primary issues is the risk of privacy breaches and potential genetic discrimination, particularly in contexts such as employment or insurance, where individuals may be unfairly treated based on their genetic risk without robust legal protections. Equally important is the need for clear and comprehensive informed consent processes that ensure individuals understand the probabilistic and non-deterministic nature of PRS. This is essential to prevent misinterpretation of genetic risk and to support informed decision-making. Furthermore, equitable access to genomic testing and counseling remains a significant challenge. Without universal or subsidized genotyping services, these advanced tools

Population	PRS validity	Notes
European	High	Source population for most GWAS
South Asian	Moderate	Higher insulin resistance despite lower BMI
East Asian	Low-moderate	Milder hyperandrogenism
African	Very low	Severely underrepresented in GWAS and PRS tools

Table 19.
Ethnicity disparities in PCOS PRS.

risk becoming accessible only to privileged populations, thereby exacerbating the existing healthcare disparities. Addressing these concerns through policy frameworks, public engagement, and ethical oversight is crucial to the responsible implementation of PRS in clinical settings.

6.3 Data integration and interoperability

Interoperability is a critical enabler for the successful integration of genetic data, clinical records, and digital health information in the development and deployment of AI-driven models for PCOS and other complex diseases. Achieving seamless data integration requires adherence to standardized frameworks such as the Observational Medical Outcomes Partnership (OMOP) common data model, Fast Healthcare Interoperability Resources (FHIR) for clinical data exchange, and Variant Call Format (VCF) for genomic data representation. These standards facilitate the harmonization of diverse data types across platforms and institutions, ensuring consistency, reproducibility, and scalability. Furthermore, the use of data lakes and cloud-based platforms provides the computational infrastructure necessary for managing large-scale, multimodal datasets and deploying AI models in real-time clinical environments. Such interoperable systems are foundational to realizing the full potential of precision medicine.

7. Future directions for research and clinical translation

Emerging trends in the application of genomics and AI to PCOS research reflect a shift toward more comprehensive, inclusive, and personalized approaches. One key advancement is multi-omics integration, which combines data from transcriptomics, DNA methylation, and the microbiome to provide a layered and more nuanced understanding of disease mechanisms. This multidimensional insight enhances the identification of biomarkers and therapeutic targets. Longitudinal life-course studies represent another transformative trend, leveraging real-time data from wearable devices and mobile health applications to monitor individuals continuously. Such data can help identify critical therapeutic windows and support early intervention strategies. To address privacy concerns and improve global inclusivity, federated learning is gaining traction. This decentralized AI approach allows model training across geographically diverse datasets without the need to share sensitive personal data, thereby preserving privacy while enhancing generalizability. Additionally, genetic stratification in clinical trials is increasingly being employed to align therapeutic interventions with an individual's genetic profile, which accelerates drug development and improves treatment efficacy. Together, these trends are redefining the landscape of PCOS research and care, moving toward precision health on a global scale.

8. Conclusion

This chapter highlighted how the integration of PRS and AI is transforming the way we understand and manage PCOS. By combining genetic data from genome-wide association studies with clinical and metabolic information through AI algorithms, we can now better identify individuals at risk, tailor treatments based on specific PCOS subtypes, and move toward a more proactive approach to care. This marks a

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significant shift from traditional symptom-based diagnosis to more predictive, personalized, and participatory healthcare.

Looking ahead, the future of PCOS management is rooted in precision medicine. Imagine a healthcare system where young women can be screened early for PCOS risk using genetic data, and AI-driven tools help clinicians make informed decisions about prevention and treatment. With digital health platforms connecting patients and providers, care becomes more accessible, timely, and personalized, ultimately reducing the long-term impact of PCOS on women's health.

To make this vision a reality, we need to focus on a few key priorities. First, research must include more ethnically diverse populations to ensure that PRS models are accurate and applicable across different groups. Second, AI systems must be developed using privacy-preserving methods like federated learning, which allows collaborative model training without sharing sensitive data. Third, these tools need to be tested in real-world clinical settings through well-designed trials. Achieving this will require strong collaboration between experts in genetics, AI, medicine, and policy, as well as clear regulatory guidelines and support for implementation. With these efforts, PRS and AI can move from research to routine care, improving outcomes for millions of women with PCOS.

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Chapter 6

The Role of Imaging and Biochemistry in the Diagnosis and Management of Polycystic Ovary Syndrome (PCOS)

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Abstract

Polycystic ovary syndrome (PCOS) is a common hormonal disorder among women of reproductive age, typically presenting with features such as irregular or absent ovulation, elevated androgen levels, and the presence of multiple ovarian cysts. Both imaging techniques and biochemical evaluations are essential in supporting the diagnosis and guiding the clinical management of PCOS, offering insights into the anatomical and functional aspects of the condition. This chapter offers an in-depth overview of how imaging contributes to PCOS assessment, particularly through modalities like transvaginal ultrasound, transabdominal ultrasound, and magnetic resonance imaging (MRI), which help visualize ovarian structure and rule out alternative diagnoses. We examine the principal diagnostic frameworks for PCOS—namely, the Rotterdam, National Institutes of Health (NIH), and AE-PCOS Society criteria—underlining the necessity of a comprehensive approach that incorporates clinical presentation, laboratory findings, and imaging results. Additionally, the chapter highlights the synergistic use of imaging and laboratory tests in routine practice, underscoring their combined value in patient classification, phenotype identification, and the development of tailored treatment strategies. Imaging is also discussed in the context of treatment monitoring and risk prediction, stressing the importance of continuous assessment over time. Lastly, the chapter considers future directions in PCOS imaging, including the exploration of new biomarkers, advances in imaging technologies, and the imperative for standardized diagnostic protocols to enhance consistency and diagnostic precision.

Keywords: polycystic ovary syndrome (PCOS), diagnostic imaging, biochemical markers, hormonal imbalance, women's health

1. Introduction

Polycystic ovary syndrome (PCOS) is a prevalent hormonal disorder affecting women of reproductive age. Clinically, it is also known as hyperandrogenic

anovulation (HA) or Stein–Leventhal syndrome. This complex condition presents with a variety of symptoms, including irregular menstrual cycles, difficulties with fertility, excessive hair growth, weight gain, and the presence of multiple ovarian cysts. These manifestations can significantly affect a woman's quality of life [1, 2]. The absence of reproductive hormones LH, FSH, estrogen, and testosterone disturbs the regular menstrual cycle, thereby causing oligomenorrhoea and amenorrhea-like irregularities. This heterogeneous familial disorder rears itself at rates ranging from 8 to 13% in women and 6% in adolescent girls, according to different population studies and definition applications [3]. The clinical signs and symptoms include androgen excess alongside abnormal menstruation patterns, anovulation irregularities, and infertility. Women who suffer from PCOS face elevated susceptibility to diabetes mellitus, as well as obesity, dyslipidemia, hypertension, anxiety, and depression [4]. These health risks for PCOS patients extend from before pregnancy until after menopause.

1.1 Epidemiology and impact

Polycystic ovary syndrome (PCOS) is primarily characterized by disruptions in hormonal regulation, often accompanied by chronic low-grade inflammation, insulin resistance, and elevated androgen levels. These factors collectively impair follicle development and increase the risk of associated health issues such as type 2 diabetes and endometrial cancer. Diagnostic criteria for PCOS typically involve assessing three key aspects: signs of androgen excess, irregular or absent ovulation, and distinctive ovarian features observed *via* imaging. PCOS etiology results from genetic elements that include single-nucleotide polymorphisms (SNPs) in particular gene sequences. PCOS results from nearly 241 different gene variations [5]. The origins of PCOS are multifactorial, with a strong genetic component; over 240 gene variants, including single-nucleotide polymorphisms (SNPs), have been implicated. These genetic factors can influence ovarian thecal cell activity, steroid hormone production, and the regulation of reproductive hormones by the hypothalamic-pituitary axis. In utero, exposure to high maternal androgen levels and other epigenetic influences, such as maternal obesity, hypertension, stress, substance use, and environmental toxins, may disrupt fetal development without altering DNA sequences. These prenatal insults can result in intrauterine growth restriction, potentially predisposing offspring to insulin resistance, glucose metabolism issues, and dysregulation of hypothalamic and pituitary hormone function later in life, increasing the likelihood of developing PCOS during adolescence. PCOS development during childhood has three main environmental risk factors, including lifestyle habits and unhealthy eating practices, as well as exposure to environmental chemicals [3]. Physical inactivity together with increased BMI, which causes obesity, plays an essential role in developing PCOS. Environmental chemicals can start certain epigenetic changes that result in PCOS development. Food adulteration and high sugar content, together with AGEs concentration, are responsible for insulin resistance, which creates the conditions for PCOS development.

Hypothalamic-pituitary-ovarian axis dysfunction comprises one aspect of PCOS pathogenesis, resulting from defects in steroidogenesis, insulin resistance, and abdominal fat deposition, and hyperandrogenism, among other contributing factors. The combined effect of these defects causes the development of PCOS, according to scientific research. The increase in body mass index and fat accumulation triggers both insulin resistance and hyperandrogenism, leading to PCOS.

Weight reduction helps people avoid developing this condition. The development of adipose tissues makes theca cells within ovaries produce extra androgen that leads to hyperandrogenemia. A combination of insulin resistance and high androgen secretion triggers type 2 diabetes and obesity, which results in menstrual cycle irregularity and causes depression, infertility, and anxiety [6]. Genetic predisposition, environmental influences, obesity, and elevated androgen levels collectively contribute to the pathophysiological cascade that underpins the syndrome. These factors promote the development of hyperinsulinemia, hyperandrogenism, oxidative stress, and ovulatory dysfunction, manifesting as oligo-ovulation or anovulation.

1.2 Global prevalence trends of PCOS

Global PCOS prevalence varies between 6 and 21% due to distinct diagnostic standards as well as population, ethnic backgrounds, and geographic areas [7]. The worldwide incidence of PCOS among women of childbearing age reached 1.55 million cases in 2017 [8], while 17.23% belonged to women between 21 and 30 [9]. Medical research has shown a substantial elevation in standardized PCOS case counts throughout Asia during the last 30 years. PCOS affected 10.01% of Chinese women in 2003 when using the Rotterdam criteria, resulting in high age-standardized incidence rate increases according to studies (73.53/100,000) [10]. The fundamental feature of PCOS involves elevated metabolic difficulties among its patients. Research has demonstrated that obesity affects about 50% of women with PCOS, while impaired glucose regulation exists in 31.1% of patients, and type 2 diabetes (T2DM) occurs in 7.5% of these patients [11]. The research data indicated PCOS patients displayed a 3.26-fold elevated risk of impaired glucose tolerance (IGT) compared to healthy subjects, and their T2DM risk was elevated 2.87 times above normal controls [12]. The prevalence of metabolic syndrome among obese PCOS patients reached 47.9% compared to 15.9% among non-obese patients, while insulin resistance occurred in 27.8% of obese patients versus 7.1% in non-obese patients [13]. A subanalysis study showed that Asian PCOS patients face greater metabolic risk than others, since they have 5.2 times more IGT cases and 4.4 times more T2DM cases compared to healthy women [14]. Studies demonstrate that PCOS prevalence has increased at a global level over the past years. The high incidence of metabolic problems in PCOS women leads to severe lifelong health consequences for their population.

The diagnosis of PCOS becomes difficult because its clinical features, such as hyperandrogenism and irregular periods, and ovarian cyst patterns, match symptoms seen in other medical conditions. Acne and hirsutism, as well as other endocrine disorders, typically exhibit similar symptoms [15]. The diagnostic process for PCOS in adolescents becomes difficult because natural puberty can produce symptoms such as irregular periods and acne, which exist in PCOS [16]. The clinical manifestations of PCOS change throughout a female's reproductive period because symptoms might vary when she enters puberty and approaches menopause [17]. The diagnostic techniques for PCOS require specific customization because ethnic differences affect how symptoms appear and how severe they become. The symptoms and metabolic characteristics of PCOS differ among various ethnic populations. The diagnostic process becomes more challenging because early life androgen exposure and genetic predispositions produce diverse PCOS symptoms [18]. The substantial obstacles in diagnosing PCOS can be overcome because machine learning and genomic research provide new ways for precise diagnosis. The combination of these technological

approaches makes it possible to create subtype-based therapeutic plans and early detection programs for various population groups [15].

2. Diagnostic criteria of PCOS

The Rotterdam criteria, introduced in 2003, serve as a globally accepted diagnostic guideline for identifying polycystic ovary syndrome (PCOS). According to these criteria, a diagnosis is made when at least two of the following three features are present after ruling out other potential causes: irregular or absent ovulation, elevated androgen levels (either observed clinically or confirmed biochemically), and polycystic ovarian appearance on ultrasound [19, 20]. Irregular ovulation, known as oligo-ovulation, indicates inconsistent menstrual cycles and may reflect dysfunction in the hypothalamic-pituitary-ovarian pathway. Anovulation refers to the complete cessation of ovulation, often contributing to infertility and menstrual disturbances [21]. Hyperandrogenism can manifest through visible signs such as excessive hair growth, acne, or hair thinning or through lab findings showing elevated androgen levels, typically stemming from the ovaries or adrenal glands. Ultrasound-based identification of polycystic ovaries involves the detection of 12 or more follicles measuring 2–9 mm in diameter and/or an increased ovarian volume greater than 10 mL [22, 23]. This inclusive diagnostic approach accounts for the varied presentation of PCOS, enabling diagnosis even when one characteristic is absent. By incorporating multiple phenotypes, the Rotterdam criteria highlight the syndrome's diverse hormonal, reproductive, and structural features, emphasizing the importance of a tailored diagnostic strategy [24].

Alternative diagnostic models, such as those proposed by the National Institutes of Health (NIH) and the Androgen Excess and PCOS Society (AE-PCOS), place greater emphasis on androgen excess as a core feature. The NIH guidelines, established in 1990, require both ovulatory dysfunction and hyperandrogenism for a PCOS diagnosis, thereby excluding individuals who only present with polycystic ovarian morphology. Similarly, the AE-PCOS Society criteria insist on the presence of clinical or biochemical signs of hyperandrogenism, reinforcing its central role. While these stricter definitions may omit some milder cases lacking overt androgen excess, they underscore ongoing debates surrounding PCOS classification. This divergence in diagnostic thresholds reflects the condition's complexity and the critical role hyperandrogenism plays in its underlying mechanisms [24, 25].

Diagnosis of PCOS presents considerable challenges due to overlapping symptoms with other endocrine and metabolic disorders, as well as variations in phenotypic expression across different age groups and ethnicities. Conditions such as thyroid disorders, congenital adrenal hyperplasia, and hyperprolactinemia can mimic PCOS symptoms, necessitating careful exclusion through appropriate laboratory testing and clinical evaluation. The phenotypic expression of PCOS varies significantly across different age groups, with adolescents often presenting with menstrual irregularities and acne, while women in their reproductive years may experience infertility and hirsutism, and perimenopausal women may exhibit metabolic complications. Ethnic variations in PCOS prevalence and presentation further complicate the diagnostic process, with some populations exhibiting higher rates of hyperandrogenism or metabolic dysfunction compared to others. Furthermore, obesity exacerbates the clinical presentation, highlighting the influence of environmental factors on the syndrome's

expression [26]. The overlapping symptoms with other disorders necessitate a thorough differential diagnosis, while variations across age and ethnicity require tailored diagnostic approaches.

3. Role of imaging in PCOS

3.1 Transvaginal ultrasound (TVUS)

Transvaginal ultrasound is the preferred imaging technique for evaluating ovarian morphology in women with suspected PCOS, offering superior image resolution and precise assessment of follicle count and ovarian volume. Due to its proximity to the ovaries, TVUS enhances visualization of small follicles compared to transabdominal ultrasound. According to diagnostic guidelines, polycystic ovarian morphology is identified when at least one ovary contains 12 or more follicles measuring 2–9 mm in diameter and exhibits an ovarian volume greater than 10 mL. A hallmark sonographic feature of PCOS, often observed through TVUS, is the "string of pearls" pattern—an arrangement of follicles along the ovarian periphery—indicative of impaired follicular maturation. This high-resolution imaging facilitates accurate diagnosis by confirming the presence of polycystic features and quantifying follicular parameters consistent with PCOS [27, 28].

The advantages of TVUS extend beyond its high resolution, encompassing its ability to assess other pelvic structures, such as the uterus and endometrium, providing valuable information regarding endometrial thickness and the presence of any structural abnormalities. The non-invasive nature and relatively low cost of TVUS make it a readily accessible and widely used imaging technique in evaluating PCOS, facilitating timely diagnosis and management. Additionally, image processing techniques are being developed to aid in identifying follicle size, number, and structure, potentially reducing the workload and time required for diagnosis [27]. TVUS helps in evaluating the impact of PCOS on uterine health.

3.2 Transabdominal ultrasound

Transabdominal ultrasound represents an alternative imaging approach for evaluating ovarian morphology, particularly in adolescents or women for whom transvaginal ultrasound is not feasible or appropriate. While transabdominal ultrasound offers a broader field of view and allows for assessment of the entire pelvis, its image resolution is generally lower compared to transvaginal ultrasound due to the increased distance between the transducer and the ovaries. The transabdominal approach requires a full bladder to improve visualization of the pelvic organs, which can be uncomfortable for some patients and may limit its applicability in certain clinical scenarios. Despite its limitations in image resolution, transabdominal ultrasound can still provide valuable information regarding ovarian size and follicle number, particularly in cases where the ovaries are significantly enlarged or contain numerous large follicles. It provides a complementary role in assessing the pelvic anatomy in conjunction with clinical and biochemical findings [29].

Transabdominal ultrasound serves as a valuable tool in specific clinical scenarios, such as evaluating adnexal masses or assessing pelvic pain, where a broader overview of the pelvic anatomy is required [30].

3.3 Magnetic resonance imaging (MRI)

MRI is employed as a second-line imaging modality in the evaluation of PCOS, offering superior soft tissue resolution and multiplanar capabilities compared to ultrasound, allowing for detailed assessment of ovarian morphology and exclusion of other pelvic pathologies. MRI provides a more comprehensive assessment of ovarian morphology, including the evaluation of stromal volume and the identification of subtle structural abnormalities that may not be readily apparent on ultrasound [31]. MRI serves as a valuable problem-solving tool in complex cases, such as suspected ovarian tumors or atypical presentations of PCOS, where accurate characterization of pelvic pathology is essential for guiding clinical management.

The high cost and limited availability, coupled with its longer acquisition times, restrict its use as a first-line imaging modality in the routine evaluation of PCOS.

3.4 Advances in imaging technology

Recent advancements in imaging technologies are significantly enhancing the ability to diagnose and manage polycystic ovary syndrome (PCOS). Innovative methods now offer superior visualization and quantitative assessment of ovarian structure and function. For instance, three-dimensional ultrasound provides improved measurements of ovarian volume and follicle count. Contrast-enhanced ultrasound can reveal minor vascular irregularities within the ovaries that may not be visible on standard imaging [32, 33]. Newer imaging modalities such as elastography can assess tissue stiffness, potentially aiding in the differentiation of benign from malignant ovarian lesions [33].

The development of high-resolution imaging techniques promises to refine the diagnostic accuracy of PCOS, enabling earlier detection and more personalized treatment strategies. Researchers are also exploring the integration of machine learning with diagnostic processes, including the use of peripheral blood markers to distinguish between different ovarian tumor types. These algorithms are capable of analyzing complex datasets, such as hormone profiles and ultrasound images, to detect PCOS, even at early stages. Additionally, new imaging tools like elastography are being investigated for their ability to evaluate tissue stiffness, potentially distinguishing benign from malignant ovarian abnormalities [34]. Artificial intelligence and machine learning tools are playing an increasing role in refining diagnostic accuracy. These technologies can synthesize clinical, biochemical, and radiological data to identify patterns predictive of PCOS. Ultimately, these innovations may streamline diagnostic workflows, minimize resource use, and accelerate the initiation of appropriate therapy [35].

4. Biochemical markers in PCOS

PCOS, an acute medical disorder including abnormalities in psychological, metabolic, and reproductive processes, is now the most commonly reported health problem, affecting 5–20% of women who are pregnant, although 70% of them go untreated [36, 37]. Since PCOS frequently causes a lack of ovulation, it is acknowledged as a possible risk factor for infertility [38]. The majority of women do not become aware of PCOS until they experience problems becoming pregnant [39]. Hormones control the menstrual cycle and other ovarian functions. Women's ovaries

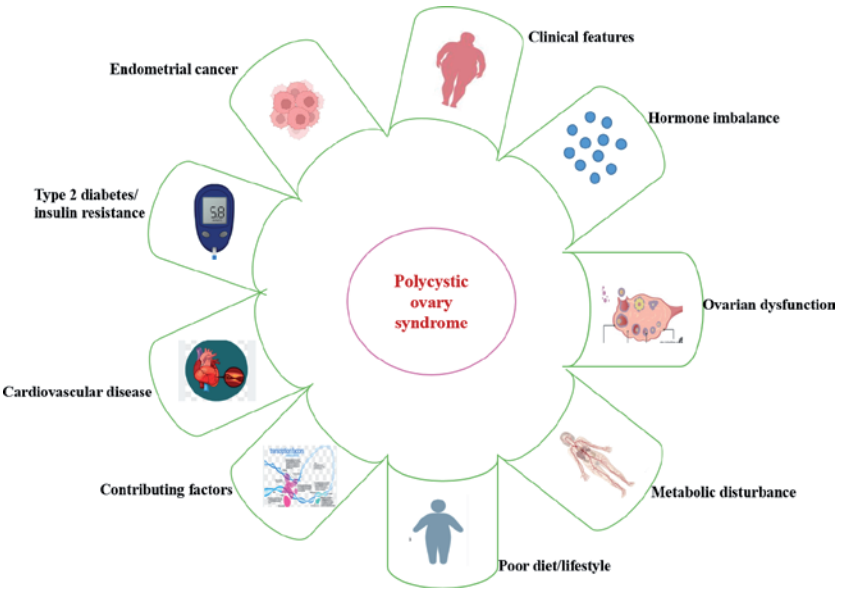

Figure 1.
Biochemical markers and other factors involved in PCOS.

malfunction when hormone levels are consistently off-kilter, which leads to the formation of an ovarian sac cyst [40]. While not all cysts are harmful, some might result in serious issues like rupture, pain, and bleeding. Menstrual issues, including amenorrhea and anovulation, can occasionally be caused by these cysts [41]. Some key hormones are directly linked to PCOS (**Figure 1**).

4.1 Hormonal profile

1. *Androgens*: Elevated androgen concentrations are a hallmark of polycystic ovary syndrome (PCOS), typically arising from altered activity within the ovaries or adrenal glands. These heightened levels of androgens are linked to the stimulation of antral follicle growth and can hinder the progression of primordial follicles to maturity [42]. Women diagnosed with the hyperandrogenic phenotype of PCOS often exhibit elevated levels of specific androgens, including androstenedione (A4), dehydroepiandrosterone sulfate (DHEAS), and testosterone (T), along with increased activity of the enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD), which plays a key role in converting precursor steroids into their biologically active forms [43, 44].

2. *LH and FSH*: In a normal menstrual cycle, LH and FSH are released by the pituitary gland from the hypothalamus. LH stimulates androgen production in the theca cells, while FSH facilitates the conversion of androgens to estrogens and supports follicular growth. In PCOS, disruptions in the hypothalamic-pituitary-ovarian axis often result in elevated LH levels relative to FSH, contributing to cyst formation [45, 46].

3. *Anti-Müllerian hormone*: Anti-Müllerian hormone, produced by granulosa cells in pre-antral and small antral follicles, is frequently elevated in PCOS [47–50].

Studies have explored the relationship between PCOS and genetic variations such as AMHR2 polymorphisms (rs2002555) and AMH SNP (rs10407022), which influence AMH expression [51], and investigated the connection between PCOS and the AMHR2 polymorphism rs2002555 and AMH SNPrs10407022 (I1e49Ser). In PCOS women, transcription factors such as FOXL2, GATA4, and steroidal factor 1 control AMH levels, leading to more follicles, higher AMH expression, and higher AMHR2 than in healthy females [52].

4.2 Metabolic assessment

1. *Insulin resistance*: This is one of the most common metabolic abnormalities in PCOS, affecting 35–80% of patients, regardless of body weight or fat distribution [53, 54]. Insulin resistance (IR), involves reduced responsiveness to insulin's metabolic actions and is a known risk factor for various health conditions. In PCOS, IR plays a central role in disease initiation and progression [55, 56]. Women with IR often exhibit higher levels of low-density lipoprotein cholesterol, reduced fasting glucose tolerance, and chronic low-grade inflammation [57].

2. *Lipid profile*: Up to 70% of women with PCOS display dyslipidemia, marked by elevated triglycerides and LDL-C and decreased high-density lipoprotein cholesterol levels. These abnormalities are tightly linked to insulin resistance. Metrics such as QUICKI, HOMA-IR, and triglyceride/HDL-C ratio are commonly used to assess insulin sensitivity. Among lipid-related indicators, the total cholesterol/HDL-C (TC/HDL-C) ratio showed the highest diagnostic accuracy in terms of area under the receiver operating characteristic (ROC) curve, sensitivity, and specificity in PCOS [58, 59].

3. *HbA1c and OGTT*: OGTT is a standard tool endorsed by the WHO for diagnosing type 2 diabetes and assessing insulin resistance [60]. The Amsterdam ESHRE/ASRM-Sponsored Third PCOS Consensus Workshop recommends OGTT screening in women with risk factors such as obesity (BMI >30 kg/m^2), family history of type 2 diabetes or gestational diabetes, hyperandrogenism, and clinical signs like acanthosis nigricans [61]. Additionally, HbA1c—a marker for long-term glucose control—was incorporated into the American Diabetes Association's diagnostic framework for diabetes risk in 2010 [62]. Elevated HbA1c levels have been observed in non-obese women with PCOS, indicating increased susceptibility to glucose intolerance [63, 64].

4.3 Inflammatory and adipokine markers

1. *C-reactive protein (CRP)*: This is an acute-phase protein synthesized by the liver in response to pro-inflammatory cytokines such as TNF-α and IL-6. It serves as a reliable marker of systemic inflammation. Elevated CRP levels are consistently observed in women with PCOS [65].

2. *Leptin*: Leptin, a hormone secreted by adipose tissue, regulates energy homeostasis and metabolic functions. As the first identified adipokine, it has been widely studied for its role in PCOS. Higher leptin concentrations are frequently correlated with insulin resistance, obesity, and increased diabetes risk among women with the syndrome [66–69].

5. Integrating imaging and biochemistry in clinical practice

5.1 Complementary roles

The integration of imaging and biochemistry plays a pivotal role in the comprehensive diagnosis and management of PCOS, offering complementary insights into the structural and functional abnormalities associated with this complex endocrine disorder.

Imaging techniques, such as transvaginal ultrasound and MRI, provide detailed visualization of ovarian morphology, allowing for the identification of polycystic ovaries, assessment of follicle number and distribution, and exclusion of other pelvic pathologies, while biochemical tests, including hormone assays and metabolic markers, reflect the underlying endocrine and metabolic dysfunction characteristic of PCOS.

The structural changes observed on imaging often correlate with the hormonal imbalances detected through biochemical testing, providing a more complete picture of the pathophysiology of PCOS.

The combined use of imaging and biochemistry facilitates a more accurate diagnosis of PCOS, particularly in women who may not meet all of the traditional diagnostic criteria, helping in confirming structural changes alongside endocrine and metabolic dysfunctions [70].

5.2 Patient stratification and phenotyping

Patient stratification and phenotyping are critical aspects of personalized treatment planning in PCOS, allowing clinicians to tailor therapeutic interventions based on the unique clinical, biochemical, and imaging characteristics of each patient. PCOS is a multifaceted disorder with varied presentations, necessitating categorization into phenotypes (A–D) according to presenting features to facilitate tailored treatment strategies [71]. Integrating clinical assessments, biochemical markers, and imaging results enables clinicians to categorize patients into specific PCOS phenotypes—namely A, B, C, and D—each defined by varying presentations of hyperandrogenism, ovulatory irregularities, and polycystic ovarian morphology. For instance, phenotype A, which includes all three features, often necessitates a treatment strategy targeting both hormonal disruptions and ovulatory dysfunction. In contrast, phenotype D, marked only by polycystic ovarian appearance, may benefit more from a metabolic-centered approach aimed at preventing long-term health complications [72]. This phenotype-based classification allows for the development of personalized treatment plans tailored to the unique clinical profile and risk factors of each patient, thereby enhancing therapeutic effectiveness and quality of life.

5.3 Diagnostic approach across age groups

The diagnostic approach to PCOS varies across age groups, reflecting the changing hormonal milieu and clinical manifestations of the disorder throughout the lifespan, with adolescents presenting with menstrual irregularities and acne, while reproductive-aged women may experience infertility and hirsutism, and perimenopausal women may develop metabolic complications.

In adolescents, the diagnosis of PCOS can be challenging due to the physiological hormonal fluctuations that occur during puberty, requiring a cautious approach that emphasizes clinical and biochemical features over imaging findings [26]. Premature diagnosis should be avoided in adolescents to avoid psychological distress, as PCOS signs often overlap with normal changes in puberty [73].

In women of reproductive age, PCOS is most often diagnosed based on the Rotterdam criteria, which include signs of hyperandrogenism, irregular ovulation, and the presence of polycystic ovaries [74]. Imaging becomes particularly important in this group to confirm ovarian morphology and to rule out alternative causes of infertility [75]. As women enter perimenopause, the clinical presentation of PCOS tends to shift; there is typically a reduction in androgen levels alongside an increase in metabolic disturbances. This transition calls for a diagnostic focus that prioritizes the evaluation of cardiovascular risk and the management of metabolic disorders [76].

6. Role in management and follow-up

6.1 Baseline evaluation

Baseline evaluation in PCOS is essential for comprehensively assessing the patient's clinical, hormonal, metabolic, and reproductive status, serving as a foundation for individualized management strategies and long-term follow-up, helping in understanding the pathophysiology of PCOS [77]. This thorough assessment involves a detailed medical history, physical examination, and relevant laboratory and imaging studies, including menstrual cycle patterns, hirsutism, acne, and alopecia [78]. Hormonal evaluation includes measurements of serum androgens, such as testosterone and DHEAS, as well as assessment of ovulatory function through measurement of progesterone levels or documentation of menstrual cycle abnormalities, while metabolic evaluation involves assessment of glucose tolerance, lipid profile, and insulin resistance.

Imaging techniques, particularly transvaginal ultrasound, are commonly utilized to assess ovarian structure and rule out other pelvic abnormalities. These evaluations offer a detailed understanding of the patient's health at the time of diagnosis and help in identifying potential areas for therapeutic focus [79].

6.2 Monitoring treatment efficacy

Monitoring treatment efficacy is a crucial aspect of PCOS management, involving regular assessment of clinical, biochemical, and imaging parameters to evaluate the response to therapeutic interventions and adjust treatment strategies as needed. Clinical parameters, such as menstrual cycle regularity, hirsutism, and acne, are monitored to assess the impact of treatment on androgen excess and ovulatory function, while biochemical parameters, such as serum androgens, glucose tolerance, and lipid profile, are monitored to evaluate the effects of treatment on hormonal and metabolic abnormalities. Improvement in these markers indicates that treatment is effective in managing the root causes of PCOS.

Imaging studies, such as transvaginal ultrasound, may be repeated to assess changes in ovarian morphology and follicle development, providing valuable

information on the effectiveness of ovulation induction therapies or other interventions aimed at improving fertility [80]. Regular monitoring allows for timely adjustments to treatment plans, optimizing outcomes, and preventing long-term complications, which is crucial for managing the diverse presentations and evolving needs of women with PCOS [81].

7. Future perspectives

Emerging research avenues promise to refine diagnostic precision, enhance therapeutic efficacy, and personalize management strategies for women with PCOS, addressing both reproductive and metabolic aspects of the syndrome.

7.1 Emerging biomarkers

The identification and validation of novel biomarkers hold great promise for improving the diagnosis, risk stratification, and treatment monitoring of PCOS, moving beyond traditional hormonal and metabolic markers to incorporate more sophisticated measures of inflammation, oxidative stress, and genetic susceptibility. Emerging biomarkers, such as anti-Müllerian hormone, microRNAs, and metabolomic profiles, may provide valuable insights into the underlying pathophysiology of PCOS and help to identify women at risk for specific complications [82].

These biomarkers could also be used to predict treatment response and personalize therapeutic interventions, tailoring management strategies to the unique characteristics and needs of each patient. Exploration of genetic and epigenetic factors may uncover novel targets for therapeutic intervention, paving the way for more effective and personalized treatments for PCOS [83].

7.2 Technological innovations in imaging

Technological advancements in imaging modalities, such as high-resolution ultrasound, magnetic resonance imaging, and computed tomography, are expanding the diagnostic capabilities and clinical applications of imaging in PCOS, enabling more detailed assessment of ovarian morphology, follicular development, and metabolic abnormalities. Three-dimensional ultrasound and Doppler imaging may provide a more accurate assessment of ovarian volume and vascularity, while magnetic resonance spectroscopy may offer insights into the metabolic composition of ovarian tissue.

These technological innovations hold promises for improving the early detection of PCOS, predicting treatment response, and monitoring disease progression, facilitating more precise and personalized management strategies. Future developments may include the use of artificial intelligence and machine learning algorithms to analyze imaging data and identify subtle patterns indicative of PCOS, further enhancing the diagnostic accuracy and clinical utility of imaging in PCOS [84].

Metabolomics, a powerful tool that involves the comprehensive analysis of metabolites in biological samples, has emerged as a valuable approach for identifying potential biomarkers and understanding the complex metabolic pathways implicated in PCOS [85]. By examining the unique metabolic signatures associated with different PCOS phenotypes, researchers can gain insights into the underlying mechanisms

driving the development and progression of the syndrome, as well as potentially discover novel therapeutic targets [86].

7.3 Need for standardization

Despite the significant advances in diagnostic criteria, imaging techniques, and biochemical markers for PCOS, the lack of standardization in these areas remains a major challenge, hindering the comparability of research findings and the implementation of evidence-based clinical guidelines. Standardization of diagnostic criteria, imaging protocols, and laboratory assays is essential for ensuring accurate and reliable diagnosis of PCOS, facilitating meaningful comparisons across studies, and promoting the development of effective treatment strategies [87].

8. Conclusion

Imaging modalities play a pivotal role in the diagnosis and management of PCOS, providing valuable information about ovarian morphology, follicular development, and associated structural abnormalities. Transvaginal ultrasound is the primary imaging technique used for assessing polycystic ovarian morphology, a key diagnostic criterion in the Rotterdam criteria [87]. MRI may be used in select cases to further evaluate ovarian and pelvic abnormalities or to exclude other conditions [71]. Integrating imaging findings with clinical and biochemical data is essential for accurate diagnosis, patient stratification, and personalized treatment planning in PCOS [25]. Future advancements in imaging technology, such as high-resolution ultrasound and MRI, hold promise for improving the early detection, risk stratification, and monitoring of PCOS, ultimately leading to better outcomes for affected women. The awareness of Rotterdam diagnostic criteria will allow better diagnosis and treatment [88]. PCOS is a complex syndrome that involves various glands and tissues, which can lead to imbalance and symptoms such as oligo-anovulation, hirsutism, and infertility [89]. Early diagnosis, along with proper treatment, is important [90]. The importance of addressing the symptoms from the patient's perspective is increasingly recognized in PCOS management, with novel therapies being targeted toward improving overall outcomes [91].

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Chapter 7

Amenorrhea: A General Approach to Diagnosis and Management

Zouhair O. Amarin and Omar F. Altal

Abstract

The etymology of the term menstruation relates to the moon. The words menses and menstruation are related to the Latin word for month, which originates from the ancient Greek word "mene", meaning moon. Menorrhagia refers to heavy and prolonged menstrual periods. The opposite is hypomenorrhea, which refers to light menstrual periods. When the frequency of menstruation is less than 21 days, it is described as polymenorrhea. If the frequency is more than 35 days, it is described as oligomenorrhea. Metrorrhagia refers to the situation of the cycles being irregular. This chapter will address the main aspects of the etiology, presentation, investigation, and management of amenorrhea.

Keywords: amenorrhea, menstrual disorders, etiology, investigations, therapy

1. Introduction

Primary amenorrhea is defined as the absence of secondary sexual characteristics such as growth spurt, thelarche, pubarche, and adrenarche by the age of 14; or the absence of menstruation (menarche) by the age of 16; or within 5 years of breast development (thelarche). Thelarche occurs around the age of 10.8 ± 1.1 years, and menarche occurs around the age of 12.9 ± 1.2 years [1, 2].

The Tanner classification describes the stages of thelarche and pubarche. Tanner Stage 1 corresponds to the prepubertal form, with progression to Stage 5, the full adult form, as follows:

Thelarche

Stage 1: Absence of palpable glandular breast tissue.

Stage 2: Palpable breast bud underneath the areola.

Stage 3: Palpable breast tissue beyond the areola with no areolar changes.

Stage 4: Areola forms an elevation above the contour of the rest of the breast.

Stage 5: Areola forms a single breast contour with pigmentation and nipple protrusion (**Figure 1**) [3, 4].

Pubarche

Stage 1: Absence of hair.

Stage 2: Downy type hair.

Stage 3: Scanty degree of terminal hair.

Stage 4: Terminal hair that fills the entire triangle overlying the pubic region.

Stage 5: Terminal hair spreads from the inguinal region to the thigh (**Figure 1**) [3, 4].

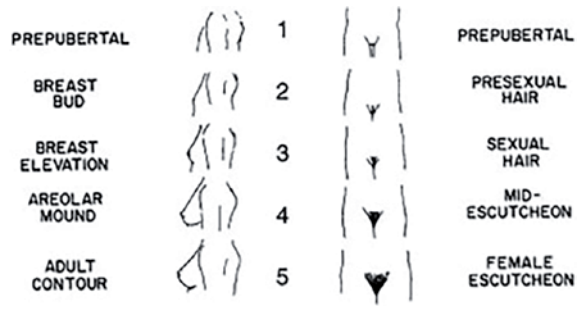

Figure 1.
Tanner stages of thelarche and pubarche [Wikipedia].

Fat and total body weight are relevant to puberty. Moderate obesity leads to the early onset of menarche. Physical training delays puberty by around 4 months per year of training [5].

Secondary amenorrhea is defined as no menstruation for more than 6 months in a female of reproductive age, outside of pregnancy [2].

2. Etiology

The etiology of amenorrhea could be chromosomal, genetic, enzymatic, or endocrine-related.

The most common cause of amenorrhea is gonadal dysgenesis, including Turner syndrome, followed by Müllerian agenesis (Mayer-Rokitansky-Küster Hauser syndrome), constitutional delay or chronic illness, polycystic ovary syndrome (PCOS), deficiency of gonadotropin-releasing hormone (GnRH), vaginal septum, weight loss, hypopituitarism, imperforate hymen, androgen insensitivity syndrome, hyperprolactinemia, prolactinoma, congenital adrenal hyperplasia (CAH), hypothyroidism, craniopharyngioma, and Cushing's disease [6–20].

Vaginal disorders that result in primary amenorrhea include cryptomenorrhea and transverse vaginal septum. Uterine disorders include cervical stenosis, Asherman syndrome, endometrial tuberculosis, and Müllerian agenesis [2].

Ovarian disorders that result in amenorrhea include premature ovarian failure, resistant ovarian syndrome, and PCOS. Polycystic ovary syndrome is a syndrome of ovarian dysfunction along with hyperandrogenism and polycystic ovary morphology. The prevalence of PCOS is 5–10% in general and is detected in around 25% of women undergoing ultrasound examinations for menstrual disorders [21–23].

The etiology of PCOS is unclear. It could be due to increased ovarian androgen production, disordered ovarian cytochrome p450 enzyme activity, increased production of luteinizing hormone (LH), insulin resistance, and family clusters. The clinical features of PCOS include oligomenorrhea, amenorrhea, hirsutism, subfertility, recurrent miscarriage, and acanthosis nigricans [21–23].

The main laboratory tests for PCOS are elevated testosterone levels, decreased sex hormone-binding globulin, elevated LH to follicle-stimulating hormone (FSH) ratio, increased fasting insulin levels, eight or more subcapsular cysts that are less than 10 mm in diameter, and increased ovarian stroma [21–23].

The treatment of PCOS includes weight loss, progesterone, combined oral contraception, and metformin. Troublesome hirsutism can be ameliorated by the use of eflornithine cream, cyproterone acetate, metformin, GnRH analogs with low-dose hormone replacement therapy (HRT), laser, or electrolysis. The long-term sequelae include diabetes mellitus and coronary vascular disease [21–23].

Thyroid disorders may lead to amenorrhea. Low levels of triiodothyronine and thyroxine stimulate the hypothalamus to secrete more thyrotropin-releasing hormone. Thyrotropin-releasing hormone stimulates the secretion of pituitary thyroid-stimulating hormone and prolactin. High prolactin inhibits GnRH release from the hypothalamus, leading to low levels of LH and FSH and amenorrhea. Hyperthyroidism may cause menstrual abnormalities, including amenorrhea [6].

Hypothalamic and pituitary causes include constitutional delay, Kallmann syndrome, weight loss, excessive exercise, craniopharyngioma, glioma, germinoma, dermoid cyst, head injuries, sarcoidosis, tuberculosis, infection, psychological stress, hypopituitarism, hyperprolactinemia, empty sella syndrome, and idiopathic causes [6].

Kallman syndrome leads to the deficiency of GnRH, anosmia, and hypogonadism. The syndrome was described in 1944 by Franz Joseph Kallmann, a German-American geneticist [24].

Drug-induced hyperprolactinemia can be caused by tranquilizers, tricyclic antidepressants, typical and atypical antipsychotics, narcotics, estrogen from combined oral contraceptives, medications used to treat gastroesophageal reflux disease, antihypertensives, hypnotics, and dopamine antagonists [25].

Other causes include chromosomal, genetic, enzymatic, and endocrine abnormalities. The differentiation of the gonads requires a tightly regulated cascade of genetic and molecular events that result in the appropriate phenotype corresponding to the given karyotype [16].

The basis of human development starts with the genotype 46XY, where fetuses develop into males, and the genotype 46XX develops into a female. The Y chromosome determines the gonadal development into testes. The testes-determining factor induces differentiation through the cell surface antigen found in individuals with Y chromosomes [6–20].

Gonadal dysgenesis, termed streak gonad aplasia, is the defective development of gonads due to fibrous tissue formation. The result is hormonal failure and the absence of secondary sex characteristics. Causes include Turner syndrome, pure gonadal dysgenesis (PGD), mixed gonadal dysgenesis, and endocrine disruptions. Turner Syndrome is the most common cause, occurring in one in 2500 births and more frequently in abortuses.

Pure gonadal dysgenesis (PGD) could present as a 46XX or 46XY karyotype. Individuals with PGD are phenotypic females with streak gonads and normal stature. The 46XX karyotype may be autosomal recessive, resulting in nerve deafness in 10% of affected individuals [26].

The 46XY karyotype or Swyer syndrome is the mutation of the SRY gene associated with the absence of testosterone-determining factor or its receptor, failure of testicular development, no androgen or Müllerian-inhibiting factor, regression of Wolffian structure, and the persistence of Müllerian structures. Individuals with Swyer syndrome are phenotypic females with normal or excessive height as a result of delayed epiphyseal closure due to low androgens or estrogens. Menstruation occurs with estrogen therapy [27].

Androgen insensitivity syndrome, also known as testicular feminization syndrome, is an X-linked trait with absent cytosolic receptors. Affected individuals

have normal breasts but no sexual hair, normal female external genitalia, an absent uterus and upper vagina, and male-range testosterone levels. Androgen insensitivity syndrome treatment includes gonadectomy after puberty and HRT, as well as vaginal dilation and vaginoplasty [28–31].

Swyer syndrome patients have poor breast development, but they have a uterus and pubic hair. Treatment consists of estradiol (30–40 picograms per milliliter) and conjugated equine estrogen (0.625 milligrams) to induce breast proliferation [27].

Other causes of amenorrhea include CAH, arrhenoblastoma, 5AR deficiency, true hermaphroditism, and absence of Müllerian-inhibiting factor [6–20].

Classical CAH is caused by 21-alpha hydroxylase deficiency and is autosomal recessive in 90% of cases. Patients present with decreased glucocorticoids and mineralocorticoids, increased sex hormones, hypotension, low sodium and high potassium levels, precocious puberty in males, and ambiguous genitalia in females. Treatment includes glucocorticoid therapy and corrective surgery [6–20].

Late-onset nonclassical CAH is most common in 21-hydroxylase deficiency. Mild forms resemble PCOS, while severe forms show signs of severe androgen excess and high 17-hydroxyprogesterone levels. Treatment includes cortisol replacement therapy and possible corrective surgery [32].

Congenital adrenal hyperplasia with 17-alpha hydroxylase deficiency leads to decreased glucocorticoids and sex hormones and increased production of mineralocorticoids, causing hypertension, high sodium and low potassium levels. Affected females lack secondary sexual characteristics. Due to low testosterone, male patients have ambiguous or entirely female external genitalia with no development of male internal genitalia and may have undescended testes. Patients need glucocorticoid and sex HRT. Fertility requires *in vitro* fertilization or embryo transfer [33].

5AR deficiency is a rare genetic condition affecting sexual development in an individual with an XY genotype. Deficiency of 5AR results in the failure of testosterone to convert into dihydrotestosterone. Patients have a vagina that may be of normal or reduced size and no uterus or cervix. Treatment may be needed to enlarge the vagina. Gonads are usually in the abdomen. Treatment includes the removal of gonads and HRT needed for females [34, 35].

Penis at 12 syndromes is caused by a mutation of the 5AR type two enzyme found in the testis of individuals with an XY genotype. Patients are born with ambiguous or female external genitalia. The uterus and cervix are absent. Testes are present but remain undescended. At puberty, testosterone levels rise significantly due to 5AR type one enzyme found in the adult liver, nongenital skin, and some areas of the brain. Low 5 AR enzyme production can also contribute to testosterone production in the testes. Treatment may include removal of gonads, HRT, or assisted reproductive technology [36].

Systemic causes for amenorrhea include common debilitating illnesses, endocrine disorders, and severe weight loss. Stress from exercise can inhibit GnRH by increasing corticotropin-releasing hormone levels, which increases adrenocorticotropic hormone (ACTH), opioid peptides, and cortisol. Corticotropin-releasing hormone (CRH) also inhibits GnRH [8, 11].

Cushing's syndrome (CS) can be either primary or secondary. Primary CS is caused by an adrenal tumor, while secondary CS is caused by ACTH hypersecretion. High CRH suppresses GnRH levels secreted by the hypothalamus. High cortisol levels lead to the suppression of steroidogenesis in the adrenal cortex, resulting in low levels of sex hormones and amenorrhea. Cushing's syndrome is diagnosed by dexamethasone suppression test at 11 pm and serum cortisol level at 8 am the next day. Diagnosis can be confirmed with a 24-hour total urine-free cortisol measurement [37].

3. History, examination, and progesterone withdrawal test

A thorough history is vital in the management of patients with amenorrhea. It includes the nature of development, age of onset of menarche in the case of secondary amenorrhea, any chronic illnesses, weight changes, excessive exercise, anosmia, medical history, surgical procedures, menopausal symptoms such as hot flushes and night sweats, past and present medications, family history of premature and early menopause, masculinizing signs and symptoms, galactorrhea, psychological status and history, and past and present stress [6–20].

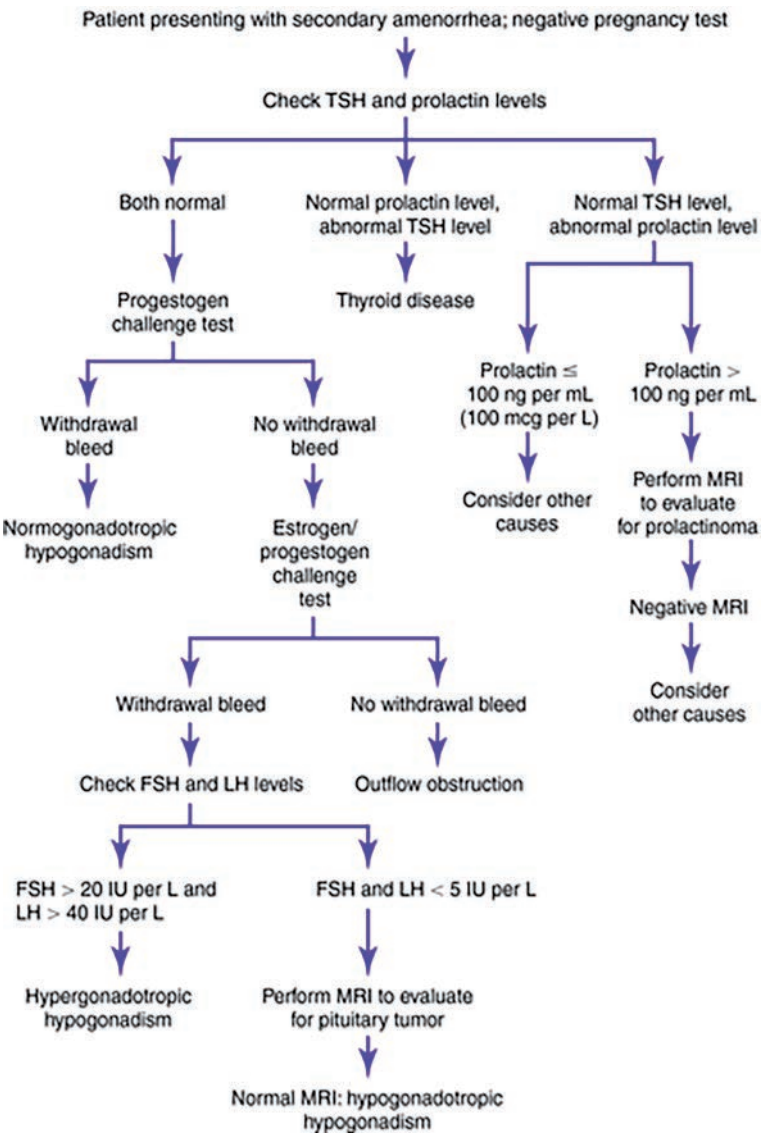

Figure 2.
First-line tests of investigating patients with amenorrhea [39].

The clinical examination would include height, secondary sexual characteristics that include thelarche, pubarche, and adrenarche; gynecological inspection and pelvic examination as appropriate; visual field assessment; and retinoscopy to evaluate the papilla for the presence of edema.

The first-line tests of investigating patients with amenorrhea include pregnancy tests, prolactin, thyroid function tests, LH, FSH, testosterone levels (below 5 nanomoles per liter), and a progesterone withdrawal test. Second-line investigations include chromosome analysis as required [6–20, 38].

The progesterone withdrawal test is performed by administering medroxyprogesterone acetate, commonly known as Provera, 10 milligrams per day for 7 days, or norethisterone, also known as Aminor, 5 milligrams per day for 7 days.

If the progesterone withdrawal test is negative, an estrogen and progesterone challenge test is performed. If the test is negative, patients are prescribed estradiol at a dose of 2 milligrams per day for 3 weeks. The test should help determine the etiology, followed by karyotyping if appropriate.

An outflow abnormality should be suspected if there is no menses. On the other hand, if there is bleeding, a hypothalamic-pituitary-ovarian axis abnormality should be suspected, and FSH and LH levels should be repeated 6 weeks later. Elevated LH and FSH levels are an indication of premature ovarian failure. If hormone levels are normal, the cause is likely hypothalamic in origin (**Figure 2**) [38].

In conclusion, amenorrhea can be an indicator of general health and well-being. Categories of amenorrhea are varied and include ovarian, endocrine disorders, and chronic disease, in addition to enzymatic and chromosomal abnormalities. History taking should include developmental abnormalities, age of menarche, weight loss, chronic illness, exercise, medical and surgical history, anosmia, current medications, galactorrhea, menopausal symptoms, family history, virilizing signs, premature menopause, stressful events, and psychological history. Physical examination should cover anthropometric and pubertal development, pregnancy test, serum prolactin, follicle-stimulating hormone, luteinizing hormone, and thyroid function test. In addition, karyotyping, serum androgen, pelvic or brain imaging, should be performed as appropriate. Treatment of amenorrhea should be conducted according to the underlying cause and can be associated with complex pathology that may require prolonged therapy that is handled with sensitivity and emotional support.

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Section 4

The Treatment of Polycystic Ovary Syndrome

Chapter 8

Treatment Options for Polycystic Ovary Syndrome

Jie Cai, Nan Lu and Jing Ma

Abstract

This chapter, in accordance with current evidence-based treatments, for Polycystic ovary syndrome (PCOS), emphasizes a lifespan, multi-phenotype patients' management model. This chapter systematically introduces therapeutic options-including lifestyle intervention, pharmacological or surgical interventions—across reproductive, metabolic, and psychological dimensions. Lifestyle intervention is highlighted as the cornerstone throughout the entire treatment process, with an analysis of the strengths and limitations of existing dietary or exercise regimens, tailored to individual patient preferences. Non-pharmacological and pharmacological approaches, including anti-obesity pharmacological agents (e.g., GLP-1RA and orlistat), and inositol will be introduced for fertility and non-infertility feature management. Also, we include pharmacological treatment attention for women in specific lifecycle (e.g., adolescence and pregnancy). It underscores a paradigm shift toward patient-centered, evidence-based practices, integrating multidisciplinary strategies to address the heterogeneous demands of individuals with PCOS.

Keywords: lifestyle intervention, pharmacotherapy, multidisciplinary management, cardiometabolic risk management, polycystic ovary syndrome

1. Introduction

Polycystic ovary syndrome (PCOS) is a prevalent and complex endocrine-metabolic disorder, affecting a significant proportion of women of reproductive age worldwide. It is characterized by a heterogeneous constellation of features, including reproductive dysfunction (ovulatory disorders and hyperandrogenism), metabolic disturbances (insulin resistance, dyslipidemia, and increased risk of type 2 diabetes), and specific morphological features on ovarian ultrasound. The management of PCOS presents a clinical challenge due to its multifaceted nature and the diverse manifestations experienced by affected individuals.

Over the past decades, the therapeutic landscape for PCOS has evolved substantially, offering a diverse array of treatment options aimed at addressing its core reproductive and metabolic dysfunctions. This diversity stems from the need to tailor interventions to the specific phenotype, predominant symptoms, and individual priorities of each patient. However, navigating this expanding range of options requires

a clear understanding of their mechanisms, efficacy, limitations, and appropriate application.

This chapter provides a systematic overview of the current evidence-based treatment strategies for PCOS. We focus on consolidating the fundamental principles guiding management and critically examining the commonly applied interventions. The cornerstone of therapy, lifestyle management encompassing structured dietary modification, targeted exercise prescription, and weight management strategies, is emphasized as the essential first-line approach for all individuals with PCOS. Beyond lifestyle, we detail the pharmacological armamentarium, including established agents like metformin for metabolic and reproductive benefits, anti-obesity medications such as GLP-1 receptor agonists and orlistat, and specific therapies for hyperandrogenic features and ovulation induction. Surgical interventions, including bariatric surgery for significant obesity and laparoscopic ovarian drilling for specific infertility scenarios, are also reviewed.

The primary objective of this chapter is to synthesize current evidence into practical guidance for managing the reproductive (e.g., anovulation and hyperandrogenism) and metabolic (e.g., insulin resistance, dyslipidemia, and obesity) features of PCOS. We underscore the importance of patient-centered, evidence-based decision-making, integrating multidisciplinary strategies to effectively address the heterogeneous needs of women with this syndrome.

2. Lifestyle management

According to the latest international evidence-based guidelines, lifestyle management constitutes the cornerstone of polycystic ovary syndrome (PCOS) management and represents the first-line therapy for affected individuals [1]. Adherence to a healthy lifestyle improves body composition, menstrual cycle regularity, multiple sex hormones, and metabolic parameters, insulin resistance, and reduces chronic low-grade inflammation in women with PCOS [2]. Lifestyle management includes, but is not limited to, weight management, dietary modification, and regular physical activity.

In overweight/obese polycystic ovary syndrome (PCOS) patients, a reduction of 5–10% from baseline body weight yields clinically meaningful health benefits. Particular emphasis should be placed on mitigating visceral adiposity and ameliorating central obesity, with targeted control of waist circumference and waist-to-hip ratio [3]. Individualized weight loss objectives must be formulated based on a comprehensive assessment of body mass index (BMI), estimated energy requirements, and physical activity expenditure. These objectives require sustained, long-term management through integrated nutritional and exercise interventions as detailed subsequently. For non-obese PCOS individuals, the primary weight management goal is weight maintenance. However, individuals whose body fat percentage exceeds 30% should aim to reduce it to within the normal physiological range. This cohort also requires vigilant, long-term strategies to prevent overweight/obesity and control excess weight gain [1].

2.1 Dietary modification

Dietary modification plays a critical role in improving anthropometric (e.g., body weight), hormonal (e.g., total testosterone levels), and metabolic (e.g., fasting glucose

levels and lipid profiles) parameters in women with polycystic ovary syndrome (PCOS). Existing evidence indicates that various dietary patterns exert beneficial effects on PCOS management [4]. However, current data demonstrate no superiority of any specific dietary composition over others in terms of anthropometric, metabolic, hormonal, reproductive, or psychological outcomes. Consequently, sustainable dietary regimens should be tailored to individual preferences and therapeutic goals in clinical practice.

2.1.1 General principles of healthful nutrition

1. Regular meal timing with controlled portions is fundamental, ensuring balanced intake across six core food groups: grains, vegetables, lean proteins, dairy, fruits, and healthy fats.

2. High-fiber foods should be prioritized, particularly unprocessed legumes and fresh vegetables.

3. Replace pro-inflammatory cooking techniques (frying/sautéing) with gentler methods such as steaming, boiling, or baking.

4. Strict limitation of dietary cholesterol sources—especially organ meats—is recommended.

5. Significant reduction in refined sugars and high-glycemic foods (e.g., sweets, sugary drinks, and desserts) is essential.

2.1.2 Managing energy intake and diet balance

1. Control Total Calories and Nutrients: Ensure enough vitamins and minerals while balancing the three main nutrients [4]:

   Carbohydrates: 40-55% total energy, primarily from whole grains (150–250 g/day) with strict limitation of high-glycemic index (GI) refined sugars (sucrose, maltose). Proteins: 15-20% total energy; strict vegetarianism is discouraged for weight management due to nutritional inadequacy risks. Lipid: 20-25% total energy; concomitantly restrict daily cooking oil consumption to 10–20 g and limit high-fat food sources.

2. Limit appetite-stimulating substances: Restrict intake of pungent spices (e.g., chili and mustard) and caffeine, which may increase hunger and food-seeking behaviors by stimulating gastric acid secretion.

Increase plant-based nutrients: Eat plenty of fresh vegetables, particularly dark leafy greens. Prepare them using water-based cooking methods like steaming, boiling, or stewing instead of frying.

Establish regular meal patterns: Regular timed meals are fundamental, with greater caloric allocation to breakfast, modest dinner portions, and fasting for ≥3 hours before sleep. Targeted management of eating disorders—particularly binge eating and food avoidance behaviors—is essential. Ensure dietary diversity through combining whole/refined grains and balancing plant/animal-based foods.

2.1.3 Different meal patterns

1. Dietary Approaches to Stop Hypertension (DASH) Protocol:

   The DASH protocol prioritizes whole grains as foundational carbohydrate sources while mandating a minimum daily intake of 1.5 kg for combined vegetables and fruits. This nutritional framework necessitates the exclusive use of skim or low-fat dairy products with strict avoidance of full-fat variants, coupled with preferential selection of white meats such as fish and skinless lean poultry cuts over red meats, animal adipose tissues, and visceral organ-derived foods. Lipid regulation involves moderate nut/legume consumption alongside significant reduction of high-fat foods and complete replacement of animal fats with vegetable oils during food preparation, with parallel rigorous restriction of refined sugars and sugar-sweetened beverages. Biochemically, this dietary pattern delivers substantial fiber, phytoestrogens, potassium, calcium, magnesium, folate, and essential micronutrients while providing bioactive compounds. Critically, evidence from multiple studies confirms the DASH diet's efficacy in improving insulin sensitivity, reducing chronic inflammatory markers, and alleviating hyperandrogenemia in polycystic ovary syndrome patients, establishing its clinical utility as a non-pharmacological intervention within comprehensive management pathways [5–7].

2. Low Glycemic Index (GI) Diet:

   The LGL Diet focuses primarily on carbohydrate sources that minimally elevate post-meal blood glucose levels. Theglycemic index (GI)—a standardized measurement system—quantifies how carbohydrates affect blood sugar responses, classifying foods as LGI when they demonstrate slow digestion and absorption. Crucially, this dietary approach not only improves hyperinsulinemia in women with polycystic ovary syndrome (PCOS) but also reduces overall body fat, with particularly significant effects on abdominal obesity [8, 9].

3. Time-Restricted Eating (TRE):

   As a circadian rhythm-aligned intermittent fasting strategy, TRE confines daily caloric intake to an 8- to 12-hour window without caloric restriction during this period [10]. Current evidence demonstrates that this time-based dietary approach improves metabolic health, suppresses inflammatory responses, and enhances circadian gene expression. These properties suggest TRE's potential as a non-pharmacological intervention for polycystic ovary syndrome (PCOS) [11]. However, clinical studies investigating TRE specifically in PCOS populations remain limited, necessitating further rigorous research to establish evidence-based clinical guidelines.

4. Ketogenic Diet (KD):

   This specialized nutritional regimen features high-fat, adequate-protein, and very-low-carbohydrate composition. Under ketosis, fat metabolism supersedes glycogen utilization, with fatty acid oxidation generating ketone bodies as primary metabolic fuel [12]. This process reduces endogenous glucose demand and

promotes rapid body mass reduction. As reported, a 3-month very-low-calorie KD intervention significantly decreased body mass and anti-Müllerian hormone (AMH) levels while substantially increasing day 21 progesterone concentrations in PCOS patients, concomitant with improved ovulatory function [13]. Although KD demonstrates promising potential as a non-pharmacological PCOS management strategy, high-quality randomized controlled trials remain imperative to establish its long-term safety and therapeutic efficacy.

2.2 Exercise intervention

As a first-line foundational therapy for both obese and non-obese polycystic ovary syndrome (PCOS) patients, exercise intervention necessitates standardized prescription principles analogous to pharmacotherapy. The exercise prescription development process comprises: conducting comprehensive assessments through medical examinations, validated questionnaires, and exercise testing to evaluate physical fitness, health status, and establish risk stratification; Establishing evidence-based therapeutic objectives; designing individualized regimens according to frequency, intensity, time, type, volume, progression principles (FITT-VP); implementing medical supervision during intervention and prescribing periodic adjustments based on physiological responses.

2.2.1 FITT-VP principle implementation

As the cornerstone of exercise prescription development, the FITT-VP framework requires detailed specification [14]:

1. Frequency (F): Frequency constitutes a foundational component of exercise prescription, referring specifically to weekly training sessions. Consistent with WHO global recommendations, three to five sessions per week—incorporating alternating aerobic and resistance modalities—allow for sufficient recovery intervals [15]. This periodization strategy facilitates overcompensation adaptation, thereby optimizing therapeutic efficacy in clinical populations.

2. Intensity (I): This critical factor determines how well an exercise plan works. To ensure effectiveness and safety, intensity must be carefully adjusted and updated over time. Exercise intensity measurement uses activity-specific methods, as detailed below:

Aerobic exercise intensity: For clinical implementation, three metrics including the heart rate reserve percentage method (HRR), metabolic equivalents (METs) values, and the rating of perceived exertion (RPE) scale are preferentially recommended:

Heart rate reserve (HRR) is defined as the difference between maximal heart rate (HRmax) achieved during exhaustive exercise and resting heart rate (HRrest). HRmax may be calculated using the validated formula: HRmax = 207 - (0.7 × Age). Consequently, HRR derivation follows: HRR = [207 - (0.7 × Age)] - HRrest. For exercise intensity prescription, target heart rate (THR) could be calculated *via* the HRR percentage method: THR = (HRR × Target Intensity Percentage) + HRrest. Aerobic exercise intensity classification standards are established as low intensity: THR < 40% HRR; moderate intensity: THR = 40-60% HRR; vigorous intensity: THR > 60% HRR [16].

For clinical illustration, consider a healthy 30-year-old female with a resting heart rate (HRrest) of 65 beats per minute (bpm) prescribed moderate-intensity exercise:

Maximal heart rate calculation: HRmax = 207 - (0.7 × 30) = 184 bpm; heart rate reserve derivation: HRR = HRmax - HRrest = 184 bpm - 65 bpm = 119 bpm; target heart range determination: THR = (HRR × Target Intensity Percentage) + HRrest; lower threshold: (119 × 0.4) + 65 = 113 bpm; upper threshold: (119 × 0.6) + 65 = 136 bpm. Thus, the prescribed target heart rate range is 113–136 bpm.

Metabolic equivalent of task (MET) is internationally recognized as the gold standard metric for quantifying absolute exercise intensity [17]. Physiologically, 1 MET is defined as the energy expenditure during seated rest, precisely equivalent to 3.5 milliliters of oxygen consumed per kilogram of body weight per minute ($3.5\ ml{\cdot}kg^{-1}{\cdot}min^{-1}$). Activity intensity is classified into three evidence-based tiers based on MET values:

Low Intensity: < 3 METs (e.g., sedentary activities: sitting quietly = 1.5 METs);

Moderate intensity: 3-6 METs (e.g., household tasks: sweeping floor = 3 METs; walking = 3-5 METs);

Vigorous intensity: ≥6 METs (e.g., running at 8 km/h = 8 METs; rope skipping = 10 METs).

Rating of perceived exertion (RPE) quantifies the holistic subjective sensation of physical strain during exercise, serving as a validated and reliable tool for monitoring individual adaptation to exercise loads. Critically, RPE serves as an intuitive self-regulation tool, enabling exercisers to autonomously modulate intensity through real-time perceived exertion monitoring. This metric is widely implemented for intensity assessment using the Borg Scale [18].

Resistance training intensity: The 1-repetition maximum (1RM) constitutes a validated metric for assessing muscular strength and serves as the foundational parameter for resistance training prescription. Defined as the maximal load an individual can lift through a full range of motion with proper form under standardized testing conditions, 1RM provides a dynamic assessment of neuromuscular capacity. For example, if a trainee can perform exactly one repetition of a dumbbell-loaded squat with 20 kg before reaching volitional failure, then 20 kg constitutes their 1-repetition maximum (1RM) for the weighted squat exercise. High-intensity strength training, equivalent to 1 to 10RM, is used to enhance the maximum contraction force of muscles. Moderate-intensity strength training, equivalent to 11 to 20RM, helps increase muscle strength and mass. Low-intensity strength training, above 20RM, is aimed at improving muscle endurance. Beginners are generally advised to use 60–70% of their 1-RM (moderate to high intensity) for interval training to build strength.

1. Exercise Time (T): Total time maintaining target exercise intensity per session.

2. Exercise-Type (T): Exercise-Type constitutes a core prescription element encompassing three modalities: aerobic exercise, resistance exercise, and flexibility exercise.

Aerobic exercise defined as rhythmic activities engaging major trunk and limb muscle groups at sustained steady-state intensity (below lactate threshold), predominantly utilizes aerobic metabolism. Exemplary modalities include brisk walking, jogging, aerobics, swimming, rope skipping, and cycling. Its principal benefit lies in

augmenting cardiorespiratory endurance—a paramount health biomarker and robust predictor of all-cause mortality. Crucially, epidemiological evidence confirms that diminished cardiorespiratory fitness represents the strongest independent risk factor for all-cause mortality, outranking hypertension, diabetes, smoking, obesity, and dyslipidemia [19].

Resistance training constitutes a form of physical activity characterized by active muscular contraction against external resistance, utilizing either body weight or specialized equipment (e.g., dumbbells, kettlebells, resistance bands, and gym apparatus). Regular implementation of this modality demonstrably enhances muscular strength, improves body composition, augments insulin sensitivity, elevates basal metabolic rate, reduces blood glucose and blood pressure levels, and contributes to metabolic syndrome prevention and management. Consequently, this intervention reduces cardiovascular risk factors and overall mortality, establishing its efficacy as a therapeutically valuable exercise approach.

Flexibility exercises constitute a foundational component of physical conditioning, functioning to increase joint range of motion (ROM) through ligamentous stretching. While not enhancing cardiorespiratory capacity or metabolic parameters, these exercises serve to augment ligament stability and neuromuscular balance, thereby reducing sports injury incidence and mitigating injury risks during physical activity. Implementation of adequate flexibility training prior to resistance training or high-intensity aerobic exercise represents an essential safety prerequisite.

1. Exercise volume (V), defined as the total amount of physical activity, is determined by the interaction of frequency, intensity, and duration parameters. For weight loss objectives, international guidelines advocate a minimum of 250 minutes of moderate-intensity or 150 minutes of high-intensity exercise weekly weight maintenance goals necessitate ≥150 minutes of moderate-intensity or ≥ 75 minutes of high-intensity weekly exercise, supplemented with muscle-strengthening activities on ≥2 days per week [1]. Adolescent PCOS patients should engage in ≥3 sessions of 60-minute moderate-to-vigorous intensity exercise weekly [20].

2. Progression (P), constitutes a core principle in exercise prescription implementation, structured across three phases: adaptation, improvement, and stabilization. Exercise specialists are required to systematically adjust prescription parameters according to these phased milestones under continuous medical supervision according to different periods of patients in the process of medical supervision.

2.2.2 Exercise prescription for polycystic ovary syndrome (PCOS)

Current evidence predominantly centers on aerobic exercise interventions for PCOS patients, with durations spanning 10 to 26 weeks [21]. Standard protocols implement thrice-weekly sessions at moderate-to-vigorous intensities. Primary outcome measures encompass alterations in cardiorespiratory endurance, sex hormone profiles, metabolic biomarkers, and body composition parameters [22, 23]. Notably, higher exercise intensities combined with extended intervention durations correlate with more pronounced improvements across all parameters. This underscores the imperative for progressive prescription strategies—systematically escalating intensity while maintaining consistency—to optimize clinical outcomes.

PCOS manifests as a highly heterogeneous endocrine-reproductive-metabolic disorder affecting individuals across BMI strata: low-weight, normal-weight, overweight, and obese. Consequently, exercise prescription requires stratification according to BMI classification and body composition phenotype. The following are the delineated prescription principles for overweight/obese PCOS versus normal-weight PCOS cohorts.

1. Exercise prescription for overweight/obese PCOS:

   The primary therapeutic objective involves weight reduction, with evidence indicating that 10% baseline weight loss within 3 months confers significant clinical benefits, while a 5-10% reduction yields discernible health improvements. Aerobic exercise constitutes the cornerstone intervention, initiated at moderate intensity: Brisk walking (5.4–6.6 km/h); Jogging (8 km/h); Recreational swimming. Exercise intensity should maintain conversational capacity ("talk but not sing" threshold). Prescribe daily exercise sessions of 20–30 minutes duration at a frequency of three to five sessions per week, with avoidance of ≥2 consecutive non-exercise days.

   With the adaptation of physical function, the intensity and time of exercise can be gradually increased, but the principle of increasing should follow the principle of first increasing the exercise time, exercise frequency, and finally increasing the exercise intensity. Duration may be extended by 5–10 minutes weekly/biweekly until the daily exercise time reaches 60 ~ 90 min and the weekly moderate intensity reaches 250 ~ 300 min. Accumulated exercise (minimum 10-minute bouts totaling 60 minutes daily) yields equivalent physiological benefits to continuous sessions.

2. Exercise Prescription for non-Obese PCOS:

   Body composition analyses in non-obese PCOS patients are commonly characterized by reduced skeletal muscle mass [24, 25]. As primary effectors of locomotion and energy metabolism, skeletal muscles serve as critical glucose disposal sites and endocrine regulators, playing indispensable roles in glycemic control and metabolic homeostasis. Consequently, resistance training is recommended to augment lean mass and neuromuscular strength, eliciting clinically significant benefits.

For novice practitioners, initial training frequency should be prescribed at two to three sessions per week, with same-muscle-group sessions separated by ≥48-hour recovery intervals to facilitate supercompensation adaptations. Implement split-body routines, such as lower-body training on Mondays and Thursdays paired with upper-body sessions on Tuesdays and Fridays. When starting resistance exercise, utilize bodyweight loading as the primary stimulus. It is recommended to use compound exercises, that is, exercises involving multiple muscle groups, such as knee push-ups, sit-ups, leg kicks, and squats. For resistance training targeting muscular hypertrophy and strength development, implement the following parameters: repetition range: 8–15 repetitions per set; movement tempo: controlled velocity (0.5-second concentric phase, 0.5-second isometric hold, 0.5-second eccentric phase); Volume: 2–4 sets per muscle group; Inter-set recovery: 1–2 minutes. Once the body adapts to current

resistance training loads, further strength and muscle gains require applying the "incremental overload" principle by gradually increasing training demands. For safety, prioritize raising repetitions and sets before increasing intensity.

It is important to note that for patients with different types of PCOS, choosing between aerobic exercise and resistance training is not an absolute choice but rather complementary. For obese patients, resistance training can be included in their exercise regimen, which helps boost the basal metabolic rate, reduce lean body mass loss, and maintain weight loss and overall metabolic stability. For normal-weight PCOS patients, those with reduced muscle mass tend to have a higher relative body fat percentage, meaning their exercise plan should balance fat reduction and muscle gain. Therefore, aerobic exercise is essential, but starting with a focus on muscle gain can make subsequent fat loss more efficient. Additionally, aerobic exercise is crucial not only for fat reduction but also for enhancing cardiorespiratory endurance, a core physical fitness component that is essential for patients with any type of disease.

3. Pharmacological treatment of metabolic dysfunctions in PCOS

3.1 Pharmacological treatment principles of metabolic dysfunctions in PCOS

Based on the 2023 PCOS Evidence-Based Guidelines [1], pharmacological treatments are not generally approved for use specifically in PCOS, and recommended use is therefore evidence-based, but off-label. For pharmacological treatment in PCOS, we would emphasize the following principles to facilitate healthcare professionals considering or recommending pharmacological therapy in PCOS patients.

Shared decision-making involving the patient (along with parents or guardians if the patient is a child) and the healthcare professional is essential. When recommending any intervention—whether alone or in combination—the individual's characteristics, preferences, and values must be carefully elicited and considered. This is particularly critical in prescribing medications, as understanding how adults and adolescents prioritize treatment outcomes significantly influences therapeutic choices. Currently, medical therapies for PCOS are generally not formally approved for this specific indication, meaning their use is evidence-based but off-label. Healthcare professionals should clearly inform patients, adolescents, and their parents or guardians about the available evidence, potential concerns, and possible side effects. Regulatory agencies are encouraged to consider approving evidence-based medications for PCOS to ensure safer and more standardized treatment options.

3.2 Metformin

3.2.1 Pharmacological mechanism of metformin

Metformin has been commonly used in women with PCOS for a long time across the world. Metformin primarily exerts its pharmacological effects by binding to presenilin enhancer 2 protein (PEN-2) within the γ-secretase complex, thereby activating adenosine monophosphate-activated protein kinase (AMPK). This triggers a cascade of downstream effects, including reduced hepatic gluconeogenesis and glucose output, enhanced glucose uptake and utilization in muscle and adipose tissue, decreased free fatty acid production, improved peripheral insulin sensitivity,

inhibition of intestinal glucose absorption, stimulation of glucagon-like peptide-1 (GLP-1) secretion, modulation of intestinal lipoprotein metabolism, and regulation of gut microbiota [26–28].

The pleiotropic effects of metformin may arise from its interactions with multiple enzymatic targets, including mitochondrial complex I of the electron transport chain, quinone oxidoreductases, vacuolar-type ATPase (V-ATPase), and AMPK [28]. Additionally, metformin inhibits M1 macrophage polarization while promoting M2 polarization and upregulates adaptive thermogenesis [27].

3.2.2 Therapeutic effects of metformin in women with PCOS

Metformin demonstrates multifaceted benefits in PCOS, including metabolic, endocrine, reproductive, and cardiovascular improvements.

1. Weight reduction: Clinical studies in PCOS patients have shown that metformin is associated with modest weight loss, though it is not superior to lifestyle interventions alone. Meta-analyses comparing metformin (850–2000 mg/day) with placebo, incorporating 26 randomized controlled trials (RCTs) with a total sample size (N = 3091). In BMI <25 kg/m^2 patients, metformin monotherapy for 3–6 months significantly reduced the waist-to-hip ratio (WHR). In BMI >25 kg/m^2 patients, metformin monotherapy led to a notable decrease in BMI [1]. Lifestyle intervention combined with metformin for 6 months further reduced WHR but did not significantly affect BMI. Oral contraceptives combined with metformin did not significantly alter BMI or WHR in adult PCOS patients [1].

2. Anti-inflammatory and immunomodulatory: Metformin exhibits anti-inflammatory and antioxidant properties [29]. Metformin monotherapy for 6 months significantly reduced C-reactive protein (CRP) levels. In pregnant PCOS patients, metformin use from early gestation until delivery increased serum IL-17 levels, suggesting immunomodulatory (rather than purely anti-inflammatory) effects, with stronger impacts in non-obese versus obese individuals [30].

3. Lipid modulating: Metformin can reduce total cholesterol (TC) and LDL-c among patients with BMI >25 kg/m^2 [31]. It can also lower triglycerides (TG) regardless of BMI stratification [7].

4. Improvement in hepatic and peripheral insulin resistance (IR): In PCOS patients with metabolic dysfunction-associated steatotic liver disease (MASLD), metformin significantly improved hepatic steatosis indices, particularly in non-obese individuals [32]. Compared to placebo, metformin can reduce HOMA-IR, fasting insulin (among BMI <25 kg/m^2 patients), and fasting glucose (among BMI >25 kg/m^2 patients) [1]. Combining metformin with oral contraceptives reduced insulin levels and HOMA-IR independently of glycemic changes [1, 33].

5. Cardiovascular risk reduction: Metformin significantly decreases carotid intima-media thickness (CIMT) in PCOS patients [34]. In PCOS patients with baseline endothelial dysfunction, 3-month metformin therapy improved endothelial function, independent of metabolic improvements [35]. However, long-term cardiovascular outcome data remain limited.

6. Ovulation restoration and androgen reduction: Metformin enhances insulin sensitivity, reducing ovarian androgen production, thereby restoring ovulation and improving natural conception rates. Anti-Müllerian hormone (AMH) levels decreased after higher metformin doses and ≥ 3-month therapy treatment [36]. In BMI <25 kg/m^2 patients, metformin lowered free androgen index (FAI), testosterone, and increased ovulation and clinical pregnancy rates, particularly in clomiphene-resistant PCOS patients [37].

7. Endometrial cancer risk reduction: Metformin exerts endometrial protective effects *via* indirect ways like lowering insulin and glucose levels, restoring cyclic estrogen-progesterone fluctuations. Metformin can also have direct effects on inhibiting endometrial cell proliferation [1, 38]. After 16 weeks of metformin combined with lifestyle intervention, PCOS-specific endometrial pathology improved *via* modulation of integrin signaling pathways [39].

3.2.3 General principles of metformin treatment

1. Dosage and duration:

   Metformin therapy should be initiated at a low dose and gradually increased to minimize gastrointestinal side effects. Starting from 500 mg twice daily or 850 mg once daily, taken with meals to enhance tolerability. Increase metformin dosage by 500 mg weekly or 850 mg every 2 weeks until reaching the target dose (1000–2000 mg/day) or the maximal tolerated dose. The maximum recommended dose for adults is 2550 mg/day. For doses >2000 mg/day, splitting the dose across two to three meals or using extended-release formulations is advised to improve adherence [30]. A minimum of 3–6 months is recommended to assess therapeutic response, with goals including: normalization of blood glucose in hyperglycemic patients, ≥5% weight loss in obese individuals [1]. If targets are not met after 3–6 months, consider combination therapy (e.g., adding insulin sensitizers, anti-androgens, or GLP-1 receptor agonists) or switching to alternative agents (e.g., inositol, COCs for hyperandrogenism).

2. Precautions:

   Metformin is contraindicated in the following conditions: hepatic dysfunction (serum transaminases over 3× upper limit of normal or severe liver dysfunction), renal dysfunction (discontinue if eGFR <45 mL/min/1.73m^2), hypoxic conditions (acute/unstable heart failure, recent myocardial infarction, severe infections, etc.), acute metabolic acidosis, diabetic ketoacidosis, acute alcohol intoxication, severe hypoxia.

3. Side effects include: Gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain; usually transient), vitamin B12 deficiency (up to 30% of long-term users), taste disturbances, and mild anorexia. Rare complications include: lactic acidosis (<0.1 cases/1000 patient-years), allergic reactions (rash, urticaria), headache, and dizziness.

3.2.4 Metformin in PCOS women with specific lifecycle

1. *Adolescents:*

Current evidence supporting metformin's benefits in adolescents (ages ≥10 years) with PCOS primarily derives from studies with small sample size with low evidence quality [1, 40]. Meta-analyses indicate that compared to combined oral contraceptives (COCs), metformin (1700–2000 mg/day) can improve BMI, TC, LDL-c, and glucose control. Some studies suggest metformin may restore menstrual regularity and reduce androgen levels in overweight/obese adolescents with PCOS. Thus, metformin is recommended as an adjunct to lifestyle intervention in adolescents with metabolic alterations in PCOS, particularly when COCs are contraindicated or poorly tolerated. Metformin may be used alone for menstrual cycle regulation [41, 42].

Suggested notes: dosage: 1500–2000 mg/day. Minimum duration: 3–6 months [43]. Approved for ages ≥10 years.

2. *Pregnancy:*

Although metformin is classified as a Category B drug in pregnancy, it can cross the placental barrier with uncertain long-term effects of fetal exposure [44]. Meta-analyses from the 2023 PCOS Evidence-Based Guidelines have demonstrated decreased preterm birth, maternal weight gain, and increased term delivery, neonatal head circumference for non-diabetic PCOS patients receiving metformin throughout pregnancy [1] for PCOS patients with T2DM receiving metformin-insulin combination therapy, increased incidence of small-for-gestational-age infants, larger arm circumference, and thicker skinfolds at 2 years of age [43, 45]. Current international guidelines do not recommend routine metformin use in pregnant PCOS patients, favoring lifestyle interventions as first-line therapy for metabolic management [1, 46]. However, individualized approaches may be considered based on patient individualized condition and with fully informed consent:

PCOS with DM Controlled by Metformin Alone Preconception: Discontinue metformin upon pregnancy confirmation (by the end of the first trimester). Transition to insulin with lifestyle modification. Continue metformin only if insulin is refused.

PCOS with Prediabetes/IR on Metformin Preconception: Discontinue metformin by the end of the first trimester, initiate insulin if GDM/ODM develops. Metformin continuation requires informed consent if insulin is refused.

PCOS Patients Using Metformin for Fertility Treatment: Discontinue immediately upon pregnancy confirmation. Must stop by the end of the first trimester at the latest.

Pregnancy in PCOS with DM: Insulin remains first-line therapy. Metformin may be added for insulin-resistant cases failing dose escalation (with informed consent).

Normoglycemic PCOS with Excessive Weight Gain/Preterm Risk: consider metformin to control gestational weight gain or reduce preterm birth. Requires absence of contraindications and informed consent.

3.3 Perimenopause or menopause

Androgen levels typically decline with age [47]; however, elevated androgen levels were observed in perimenopausal or post-menopausal PCOS patients [48]. These patients frequently experience progressive weight gain, increased abdominal adiposity, exacerbated obesity, and lifelong cardiometabolic risks after menopause [49, 50]. So, metformin is still recommended to manage metabolic abnormalities in this population.

Suggested Notes: The dosing regimen and treatment duration should follow the same guidelines as for reproductive-age PCOS patients without fertility concerns (500–2000 mg/day). Evaluating response every 3–6 months. Particular attention should be paid to this population on polypharmacy risks of drug interactions, age-related comorbidities, liver/kidney function monitoring, and cardiovascular risk evaluation.

3.4 Anti-obesity pharmacological agents

Obesity represents a major clinical challenge in both adolescent and adult populations with polycystic ovary syndrome (PCOS), exhibiting significantly higher prevalence rates compared to non-PCOS individuals. Although lifestyle modification remains foundational for weight management in PCOS, emerging evidence highlights the potential adjunctive role of pharmacotherapeutic agents in achieving sustainable weight reduction and metabolic improvements, particularly in high-risk populations. To cover the limitations of lifestyle interventions alone, including issues with long-term adherence and efficacy. Recent systematic reviews and international guidelines have evaluated anti-obesity medications (AOMs) in general and high-risk populations. Several agents—such as GLP-1 receptor agonists (GLP-1 RA) and lipase inhibitors (orlistat)—have gained regulatory approval for weight management in adults, though accessibility remains limited by cost and regional availability disparities.

3.4.1 GLP-1 analogs and GLP-1RA

3.4.1.1 Pharmacological mechanism of GLP-1

Improvement of Insulin Resistance: Glucagon-like peptide-1 (GLP-1) is an incretin hormone that enhances glucose-dependent insulin secretion and exerts multiple metabolic regulatory effects. GLP-1 analogs and GLP-1RAs ameliorate insulin resistance through several mechanisms: appetite suppression, reduced food intake, delayed gastric emptying and gastrointestinal motility, increased energy expenditure, promotion of white adipose tissue browning, as well as improvement of lipid profiles, attenuation of inflammatory responses, and reduction of oxidative and endoplasmic reticulum stress [51–54]. Furthermore, GLP-1RAs directly modulate insulin signaling pathways to enhance insulin sensitivity, facilitate glucose uptake, and stimulate pancreatic β-cell proliferation.

Regulation of Hypothalamic-Pituitary-Ovarian (HPO) Axis Function: GLP-1 receptors are widely expressed in the hypothalamus, pituitary gland, ovaries, and endometrium [55, 56]. GLP-1 can stimulate GnRH and LH secretion by modulating GABAergic inputs and Kiss-1 neuronal activity [57]. Central administration of GLP-1 rapidly elevates preovulatory LH levels, subsequently increasing estrogen

and progesterone concentrations while augmenting the number of mature follicles. Additionally, GLP-1RAs inhibit multiple progesterone-synthesizing enzymes and upregulate FSHR expression in granulosa cells, while concurrently exerting anti-inflammatory and anti-fibrotic effects in ovarian and endometrial tissues. These findings demonstrate GLP-1's direct regulatory effects on the HPO axis. Moreover, through weight reduction, GLP-1RAs may partially reverse obesity-induced suppression of GnRH and LH secretion, thereby indirectly modulating HPO axis function [57–59].

Reduction of Systemic Chronic Inflammation: GLP-1 and its analogs exhibit anti-inflammatory properties across multiple organs and tissues, including adipose tissue, vascular endothelium, liver, and brain. These compounds decrease pro-inflammatory cytokines (such as IL-6, IL-1, TNF-α, MCP-1, and NF-κB) while enhancing the secretion of anti-inflammatory factors like adiponectin. GLP-1RAs also ameliorate obesity- and T2DM-associated neurovascular uncoupling and microvascular dysfunction, leading to cognitive improvement, effects primarily mediated through their anti-inflammatory mechanisms [60–65].

3.4.1.2 Types of GLP-1 analogs and GLP-1RA

GLP-1RAs can be categorized based on structural classes: (i) non-human analogs (exendin-4-based) including exenatide, exenatide extended-release, lixisenatide, and pegylated loxenatide; (ii) human analogs (native GLP-1-based) including liraglutide, dulaglutide, albiglutide, and semaglutide; and (iii) fully human GLP-1 (benaglutide). Pharmacokinetically, these agents are classified as ultra-short-acting (benaglutide, requiring TID dosing), short-acting (exenatide and lixisenatide, BID dosing), long-acting (liraglutide, QD dosing), and ultra-long-acting (dulaglutide, exenatide ER, and pegylated loxenatide, weekly dosing).

Currently, liraglutide and semaglutide have received FDA approval for obesity management (BMI ≥30 kg/m^2 or ≥ 27 kg/m^2 with weight-related comorbidities). Benaglutide represents the first agent developed specifically for Chinese overweight/obese populations (BMI ≥28 kg/m^2 or ≥ 24 kg/m^2 with comorbidities like dysglycemia, hypertension, or dyslipidemia).

While existing PCOS research primarily focuses on liraglutide and exenatide, current evidence remains limited by small sample sizes and predominance of open-label studies. These limitations highlight the need for larger, controlled trials to establish the therapeutic role of GLP-1RAs in PCOS management.

3.4.1.3 General principles of GLP-1 analogs and GLP-1RA treatment

The therapeutic window for GLP-1RAs in PCOS requires balancing metabolic benefits with careful monitoring of body composition changes and potential adverse effects. Regular follow-up is crucial to optimizing outcomes while minimizing risks. During GLP-1 analog/GLP-1RA therapy, careful dietary monitoring is essential due to the medications' appetite-suppressing effects. Patients should maintain adequate-protein intake (1.0–1.5 g/kg ideal body weight) to prevent muscle loss, prioritize high-quality protein sources, and adjust to 0.8 g/kg for patients with renal impairment (proteinuria or reduced GFR).

Common side effects include: gastrointestinal symptoms (nausea, diarrhea, vomiting, constipation, and abdominal pain), headache, upper respiratory infections,

and hypoglycemia. These symptoms typically diminish within weeks of continued treatment. Pancreatitis requires immediate discontinuation.

Combination therapy considerations: when combined with metformin, patients could maintain standard metformin dosing if tolerated. Or dose reduction for significant GI intolerance should be considered.

Follow-up should include: Anthropometric measurements (weight, body composition, waist/hip circumference), treatment efficacy (target 5–10% weight reduction), medication adherence, PCOS-specific endocrine parameters, and safety monitoring.

Contraindications: Allergic to drug components, type 1 diabetes or diabetic ketoacidosis, personal/family history of medullary thyroid carcinoma (MTC), multiple endocrine neoplasia syndrome type 2 (MEN2), severe renal impairment (eGFR <30 mL/min), severe hypertriglyceridemia (TG ≥5.56 mmol/L), or significant gastrointestinal disorders (gastroparesis, IBD, and cholelithiasis).

3.4.2 GLP-1 analogs and GLP-1RA treatment during specific lifecycle

3.4.2.1 Adolescents

Approximately 70% of prepubertal obesity cases persist into adulthood, emphasizing the critical need for effective early-life interventions [66]. Nearly 50% of adolescents achieved ≥5% BMI reduction with liraglutide therapy. In obese adolescents unresponsive to lifestyle modification alone, liraglutide 3.0 mg plus lifestyle intervention significantly reduced BMI SDS compared to placebo [20, 66]. That evidence demonstrates the potential of GLP-1RAs in adolescent weight management.

Current approvals of GLP-1 include:

FDA (2019): Liraglutide for T2DM (≥10 years) and obesity (≥12 years, BMI ≥ 30 kg/m^2, weight > 60 kg);

FDA (2021): Semaglutide 2.4 mg for obesity (≥12 years, BMI ≥ 95th percentile).

Adolescents may consider 3–6 months of GLP-1RA therapy after a comprehensive evaluation and informed consent discussion with their guardians.

3.4.2.2 Preconception or pregnancy

The 2023 International PCOS Guidelines emphasize preconception assessment and education to mitigate pregnancy risks [1]. A pilot RCT (n = 28) showed liraglutide 1.2 mg/day + metformin for 12 weeks improved IVF outcomes vs. metformin alone [67]. A larger trial (n = 176) demonstrated higher natural conception rates after transitioning from exenatide to metformin versus metformin alone [68]. For overweight/obese PCOS patients with inadequate response to lifestyle + metformin, adding short/ultra-short-acting GLP-1RAs for 3 months with contraception can benefit metabolic and weight management. However, caution should be taken that GLP-1RAs were classified as Category C in pregnancy, so effective contraception is mandatory during treatment.

Suggested notes: Target 5–10% weight reduction and avoid excessive weight loss. During GLP-1RAs therapy, PCOS patients are advised to maintain protein intake (1.0–1.5 g/kg) to preserve lean mass. Effective contraception is mandatory, and at least five half-lives' washout time is needed before pregnancy. Due to the safety uncertainty, GLP-1RAs are not suggested during pregnancy.

3.4.2.3 Perimenopause or menopause

Women with PCOS face elevated risks of increased cardiovascular risks in postmenopausal PCOS such as hypertension, type 2 diabetes, dyslipidemia, and non-fatal cerebrovascular events [69]. These risks persist beyond reproductive years, with postmenopausal PCOS women showing progressive worsening of insulin resistance, increased carotid intima-media thickness, higher incidence of myocardial infarction/angina, and persistent hyperandrogenemia exacerbating metabolic dysfunction [70]. While most PCOS studies focus on reproductive outcomes, emerging evidence suggests GLP-1RAs' cardiovascular benefits. So GLP-1RAs for postmenopausal PCOS management could improve lipid profiles, carotid IMT, body weight management, and glucose control.

3.4.3 Orlistat

1. Pharmacological mechanism and therapeutic effects of orlistat

Orlistat is a reversible inhibitor of gastrointestinal lipases. Orlistat exerts its effects through competitive inhibition of pancreatic and gastric lipases. By binding covalently to the active serine site of these enzymes, orlistat prevents the hydrolysis of dietary triglycerides into absorbable free fatty acids and monoglycerides. It can reduce dietary fat absorption by approximately 30% and increase fecal fat excretion. So, orlistat's localized action makes it a possible option for PCOS patients with obesity, particularly when combined with metformin and lifestyle intervention. Orlistat also exerts beneficial metabolic effects (improves insulin sensitivity, reduces LDL-C and TC) among PCOS women secondary to weight/fat loss. A study with a small sample size also showed that orlistat modestly lowers androgen levels.

2. General principles of orlistat treatment

Orlistat complements metformin's insulin-sensitizing effects by targeting dietary fat metabolism. Orlistat (120 mg capsule) is taken with each main meal (up to three times daily) or within 1 hour after eating. Omit the dose if a meal is skipped or contains no fat. However, there is no direct effect on glucose metabolism (unlike GLP-1RAs or metformin). Gastrointestinal side effects (steatorrhea and bloating) are common. Fat-soluble vitamins (A, D, E, and K) malabsorption may exist; supplementation is required.

3.5 Dietary supplements

3.5.1 Inositol

Inositol: Inositol, also known as cyclohexanehexol, is a water-soluble vitamin and essential physiological compound. Its predominant isoforms are myo-inositol (MI) and D-chiro-inositol (DCI). These natural molecules are safe and well-tolerated and have insulin-sensitizing activity. In addition, MI mediates FSH signaling. Research confirms that in PCOS patients, MI and DCI significantly enhance insulin sensitivity by reducing the Homeostatic Model Assessment (HOMA) index [71]. Furthermore, myo-inositol supplementation matches metformin's efficacy in restoring menstrual

regularity and ovulation [72]. Evidence supports myo-inositol supplementation (4 g daily) as an alternative to metformin for PCOS patients seeking to improve insulin resistance and menstrual irregularities, particularly when guided by individual tolerance or preference [73].

3.5.2 Vitamin D

Vitamin D enhances insulin synthesis and secretion, improves insulin sensitivity, and inhibits inflammatory responses. It regulates progesterone, estradiol, and testosterone synthesis while normalizing ovarian anti-Müllerian hormone (AMH) levels, thereby improving ovulation. Additionally, it modulates placental, endometrial, and fallopian tube epithelial cells to enhance reproductive function. About 65–80% of PCOS patients exhibit vitamin D deficiency (serum 25(OH)D < 30 ng/ml) [29]. Vitamin D supplementation reduces testosterone, DHEAS, cholesterol, and triglyceride levels, with recommended daily doses of 2000–4000 IU [74, 75].

3.5.3 Folic acid

Folic acid (vitamin B9), a water-soluble vitamin, demonstrates antioxidant, anticancer, cardiovascular, and neuroprotective properties. Evidence indicates that PCOS patients with elevated homocysteine benefit from supplementation, which reduces homocysteine levels, enhances antioxidant capacity, and improves insulin resistance [76]. Recommended therapy involves weekly folic acid doses of 1–5 mg, with homocysteine monitoring until normalization, followed by discontinuation.

4. Pharmacological treatment of reproductive features in PCOS

4.1 Anti-androgen pharmacological agents

Oral anti-androgen pharmacological agents (spironolactone, cyproterone acetate, finasteride, and flutamide) can be used to treat hirsutism, acne, and hair loss.

Spironolactone is a potassium-sparing diuretic that competitively inhibits aldosterone receptors while exerting significant antiandrogenic effects. This medication antagonizes androgen receptors and suppresses androgen production by inhibiting key steroidogenic enzymes, including 17β-hydroxysteroid dehydrogenase (which converts androstenedione to testosterone) and 5α-reductase (responsible for testosterone to dihydrotestosterone conversion). For patients over 20 years of age, the recommended dosage ranges from 100 to 150 mg daily, with gradual dose titration advised to minimize potential adverse effects such as electrolyte imbalances and hypotension. Optimal administration involves morning dosing with meals to enhance bioavailability, reduce gastrointestinal discomfort, and prevent sleep disturbances from nocturia. Clinicians should regularly monitor blood pressure, heart rate, and serum electrolytes during treatment. Spironolactone is contraindicated in patients with hyperkalemia, renal or hepatic impairment (due to risk of electrolyte-induced complications including hepatic encephalopathy), hyponatremia, or metabolic acidosis [1].

The medication's dual mechanism as both a diuretic and anti-androgen makes it particularly valuable for managing conditions involving aldosterone excess or hyperandrogenism. Its potassium-sparing properties necessitate careful patient selection

and monitoring, especially in those with predisposing factors for electrolyte disturbances. The recommendation for morning administration and gradual dose escalation reflects clinical experience in balancing therapeutic efficacy with tolerability, while concomitant food intake serves to both improve drug absorption and minimize gastrointestinal side effects. Regular laboratory assessment of potassium and sodium levels is essential given the drug's potential to alter electrolyte homeostasis, particularly in vulnerable populations.

Finasteride is a synthetic steroidal compound that functions as a selective inhibitor of type II 5α-reductase, the key enzyme responsible for converting testosterone to its more potent metabolite dihydrotestosterone (DHT). By blocking this peripheral conversion process, finasteride significantly reduces DHT concentrations in both serum and target tissues. The therapeutic rationale for its use in androgenetic alopecia stems from the well-documented presence of type II 5α-reductase in human hair follicles and the pathological observation that miniaturized follicles in balding scalp areas exhibit elevated DHT levels. Clinical administration of finasteride (5 mg once daily, with no food restrictions) produces measurable decreases in both scalp and circulating DHT concentrations, leading to three distinct therapeutic effects: stimulation of new hair growth, increased hair density, and prevention of further hair loss. The full clinical response typically requires at least 3 months of continuous therapy, with optimal results emerging over longer treatment durations. Importantly, the drug's effects are maintenance-dependent, as discontinuation leads to gradual reversal of benefits within 12 months due to restored DHT production. This pharmacokinetic profile underscores the necessity for ongoing treatment to sustain therapeutic outcomes in androgen-dependent alopecia.

4.2 Combined oral contraceptives (COCs)

All short-acting oral contraceptives can be employed for hyperandrogenism treatment, with progressive improvements from first to third generation formulations demonstrating enhanced progestin activity and more natural progesterone-like effects. When administered cyclically for 3–6 months or longer, COCs effectively achieve the following therapeutic objectives: correction of biochemical hyperandrogenemia, amelioration of androgen-dependent clinical manifestations, and endometrial protection through regular withdrawal bleeding that reduces endometrial cancer risk.

Diane-35 (ethinyl estradiol 0.035 mg/cyproterone acetate 2 mg): The 17-hydroxyprogesterone derivative cyproterone acetate (CPA) exerts multimodal antiandrogenic effects *via* competitive binding at androgen receptors, suppressing LH-dependent thecal cell androgen production, inhibiting 5α-reductase activity, and accelerating testosterone clearance. Complementing these actions, the ethinyl estradiol component elevates sex hormone-binding globulin (SHBG) levels, thereby reducing circulating free testosterone. This dual mechanism makes Diane-35 particularly effective for managing moderate-to-severe inflammatory acne (papulopustular/nodulocystic forms), androgenetic alopecia, mild hirsutism, and other PCOS-related hyperandrogenic manifestations.

Marvelon (desogestrel 0.15 mg/EE 0.03 mg): This second-generation COC primarily acts through suppressing the pituitary-gonadal axis (reducing LH/FSH secretion) and menstrual cycle regularization. Administration begins on cycle day 1, with 21 active pills followed by a 7-day hormone-free interval. Common initial side effects (nausea, headaches, breast tenderness, breakthrough bleeding) typically resolve within three

cycles. Rare but serious adverse effects include thromboembolic events, particularly in patients with predisposing factors.

Yasmin (Drospirenone 3 mg/EE 0.03 mg): The unique properties of drospirenone, a spironolactone analog, include minimal androgenic activity, antimineralocorticoid effects counteracting estrogen-induced fluid retention, and potential benefits for premenstrual syndrome. While advantageous for non-hyperandrogenic PCOS patients, its weaker antiandrogenic effects compared to CPA limit its utility in overt hyperandrogenism. The thromboembolic risk profile necessitates careful patient selection, particularly in smokers or those with metabolic comorbidities.

4.2.1 Safety considerations and contraindications

Active/past thromboembolic disorders, high thrombogenic risk profiles, migraine with aura, uncontrolled hypertension, estrogen-dependent malignancies, severe hepatic dysfunction, and pregnancy/lactation.

4.2.2 Progestin monotherapy and sequential therapies

Progestin monotherapy is indicated for anovulatory patients without hyperandrogenism/insulin resistance, endometrial protection without contraceptive needs. Medroxyprogesterone acetate (10 mg/day for 10–14 days monthly) induces regular withdrawal bleeding while modestly reducing LH pulse frequency. This approach lacks metabolic or ovarian morphological benefits.

4.2.3 Estrogen-progestin sequential therapy

This physiological hormone replacement regimen is indicated for those PCOS patients with hypoestrogenemia, adolescent dysfunctional uterine bleeding, and non-hyperandrogenic PCOS without fertility goals. Standard protocol is estradiol valerate 2 mg/day (days 1–21), Medroxyprogesterone acetate 10 mg/day (added days 11–21), then with a 7-day hormone-free interval.

Dose adjustments based on endogenous estrogen levels may reduce estrogen components by 50–75%.

4.3 Ovulation induction therapies for PCOS-related infertility

Clomiphene Citrate (CC): CC remains the cornerstone of ovulation induction in PCOS patients, with over 50 years of clinical application validating its efficacy and safety profile. As a selective estrogen receptor modulator (SERM), CC works by competitively binding to hypothalamic estrogen receptors, thereby disrupting negative feedback and increasing FSH secretion. The standard protocol initiates with 50 mg daily for 5 days, typically beginning between cycle days 2–5 following either spontaneous or progestin-induced withdrawal bleeding. Careful dose titration is paramount - approximately 45% of patients will ovulate at 50 mg, with cumulative ovulation rates reaching 70–75% at 100 mg and 80–85% at 150 mg daily. Monitoring should assess both follicular development (*via* ultrasound) and luteal phase adequacy (through mid-luteal progesterone levels), as a shortened luteal phase (<11 days) may indicate suboptimal dosing. While generally well-tolerated, clinicians must remain vigilant for potential adverse effects including visual disturbances (occurring in <2% of cases), vasomotor symptoms, and the risk of multiple pregnancies (5–8%

incidence, predominantly twins). Importantly, six treatment cycles represent the therapeutic ceiling due to both diminishing returns and emerging data suggesting potential long-term effects on endometrial receptivity. For the approximately 20–25% of patients demonstrating CC resistance (failure to ovulate at 150 mg), alternative strategies must be considered [3].

Letrozole: Clinical evidence demonstrates that letrozole shows superior efficacy across multiple key outcome measures over CC. Specifically, it achieves higher ovulation rates (both per patient and per cycle), pregnancy rates, clinical pregnancy rates, and live birth rates (per patient) compared to conventional treatments. Regarding safety outcomes, comparative analyses reveal no statistically significant differences between treatment groups for secondary endpoints including multiple pregnancy rates (both per patient and per pregnancy) and miscarriage rates (both per patient and per pregnancy). Its mechanism involves temporary estrogen suppression, triggering amplified FSH release while avoiding the detrimental effects of prolonged estrogen receptor blockade characteristic of CC.

Standard dosing begins at 2.5 mg daily for 5 days (days 2–5 of the cycle), with approximately 60% ovulation rates at this initial dose. For non-responders, progressive escalation to 5 mg and ultimately 7.5 mg daily can achieve cumulative ovulation rates exceeding 90% in CC-resistant cases. Letrozole's pharmacokinetic profile offers several advantages: shorter half-life (45 hours vs. CC's 5–7 days) reduces risks of multiple follicular development, while the absence of anti-estrogenic effects on the endometrium may improve implantation rates.

Gonadotropin Therapy: Reserved for CC/letrozole failures or as part of assisted reproductive technologies, gonadotropin therapy represents the most potent ovulation induction modality [77]. Modern preparations include urinary-derived products (hMG, containing both FSH and LH activity) and highly purified/recombinant FSH formulations. The step-up protocol has become the gold standard, initiating at 37.5–75 IU daily with incremental 37.5 IU adjustments every 5–7 days based on follicular monitoring. This approach yields monofollicular development in approximately 70% of cycles while maintaining acceptable pregnancy rates (20–25% per cycle). The step-down alternative, beginning with 150 IU daily and then reducing based on response, may benefit selected patients with uniform follicle cohorts. Critical to success is intensive monitoring - serial ultrasounds (beginning days 6–8) and estradiol measurements help identify the 15–20% of PCOS patients at risk for ovarian hyperstimulation syndrome (OHSS). Adjuvant approaches include combining gonadotropins with metformin (reducing OHSS risk by 30%) or using GnRH antagonist co-treatment to prevent premature LH surges. Recent innovations like recombinant LH supplementation and individualized dosing algorithms based on anti-Müllerian hormone levels continue to refine outcomes. Despite advances, gonadotropin therapy remains resource-intensive, requiring six to eight monitoring visits per cycle and carrying 10–15% multiple pregnancy rates even with careful management.

Combination and Adjuvant Therapies: Innovative protocols increasingly combine ovulation induction agents to optimize outcomes. CC-gonadotropin combinations (CC 100 mg days 3–7 plus FSH 75 IU starting day 7) can reduce gonadotropin requirements by 30–40% while maintaining pregnancy rates. Letrozole-FSH protocols similarly demonstrate enhanced follicular sensitivity, particularly in obese PCOS patients. Insulin sensitizers like metformin (especially in insulin-resistant patients) and adjuvant dexamethasone (for hyperandrogenism) can improve ovulation rates by 15–20% in refractory cases [21]. Emerging evidence supports the use of laparoscopic ovarian drilling in CC-resistant patients before progressing to gonadotropins,

particularly in resource-limited settings. Regardless of protocol, all ovulation induction must be accompanied by comprehensive patient counseling regarding success rates (cumulative pregnancy rates of 60–70% over six cycles), risks (OHSS occurring in 5–8% of gonadotropin cycles), and the importance of timed intercourse or intrauterine insemination to maximize success. The treatment algorithm should progress from oral agents (CC/letrozole) to gonadotropins over four to six failed cycles, with *in vitro* fertilization considered after 12 months of unsuccessful ovulation induction.

5. Other treatment options

5.1 Bariatric surgery

Current evidence demonstrates significant metabolic and reproductive benefits of bariatric surgery in obese PCOS patients. Substantial improvements in multiple biochemical parameters, including resolution of hyperandrogenemia, insulin resistance, menstrual irregularities, and hirsutism, were reported. In higher weight categories (BMI > 35 kg/m^2), lifestyle interventions are not durably effective, whereas bariatric/metabolic surgery has been demonstrated to provide substantial durable weight loss with accompanying improvement in health, well-being and longevity [50] with guidelines recommending surgery to aid weight loss with a BMI > 35 kg/m^2 and potentially for a BMI between 30 and 34.9 kg/m^2 with associated metabolic comorbidity. The most common weight loss surgeries include Vertical Sleeve Gastrectomy and Roux-en-Y gastric bypass with minimally invasive, low morbidity and mortality. In adults and adolescents with PCOS, bariatric surgery is effective for the management of hormonal and clinical PCOS features and weight [78]. A recent large single-centre prospective cohort study was published in 993 women with PCOS [51] showing dramatic improvement in hirsutism, menstrual irregularity, and associated comorbidities [T2D (79.7%), hypertension (78.7%), sleep apnea (98.5%)] and symptoms of PCOS were statistically ($p < 0.0001$) reduced at follow-up.

However, the potential risks—including perioperative mortality (0.1–1.1%), infectious complications, intestinal obstruction, and nutritional deficiencies—must be thoroughly evaluated during preoperative assessment. The metabolic effects of surgery, particularly the amelioration of hyperinsulinemia, appear to mediate the observed improvements in both reproductive and metabolic parameters of PCOS. Current guidelines emphasize the importance of comprehensive preoperative counseling and long-term multidisciplinary follow-up to optimize surgical outcomes in this population.

5.2 Laparoscopic ovarian drilling (LOD)

The surgical management of PCOS dates to 1936 with the introduction of ovarian wedge resection (OWR), an open procedure involving the excision of one-third to one-half of both ovaries. Early studies reported promising outcomes, with 87% ovulation rates and 81% pregnancy rates in severe PCOS cases [3]. However, OWR fell out of favor due to its association with pelvic adhesions, which could convert functional infertility into structural infertility and, in severe cases, lead to permanent sterility.

LOD has since emerged as a minimally invasive alternative, offering comparable efficacy with reduced adhesion risks. The procedure involves laparoscopic thermal ablation (monopolar/bipolar electrocautery, laser, or ultrasonic energy) of ovarian

follicles, achieving multiple therapeutic effects: reduction of androgen production by destroying ovarian stroma, drainage of follicular fluid, and lowering intraovarian testosterone levels. LH levels decreased, but FSH increased due to reduced estrogen feedback. LOD can also restore ovulation, improve pregnancy rates, and lower miscarriage risk through endocrine normalization.

Despite its advantages, LOD remains an invasive procedure and with inherent risks such as anesthesia/surgical complications, postoperative adhesions, ovarian reserve reduction, and high costs compared to medical therapies. Current evidence supports LOD primarily for CC-resistant PCOS patients before progressing to IVF, particularly in resource-limited settings where gonadotropins are inaccessible.

5.3 Assisted reproductive technologies (ART)

ART therapies including intrauterine insemination (IUI), *in vitro* fertilization with embryo transfer (IVF-ET), frozen-thawed embryo transfer (FET), and *in vitro* oocyte maturation (IVM) and intracytoplasmic sperm injection (ICSI) used in male factor infertility. For PCOS patients refractory to conventional therapies, ART represent a critical therapeutic option. However, ART implementation in PCOS requires special consideration due to the characteristically high risk of ovarian hyperstimulation syndrome (OHSS) secondary to excessive follicular recruitment, necessitating modified stimulation protocols such as GnRH antagonist regimens with adjusted trigger strategies [79]. Additionally, the propensity for multifetal pregnancies from multiple embryo transfers underscores the importance of elective single embryo transfer (eSET) to mitigate obstetric risks. While procedural complications including infection and ovarian torsion remain concerns, emerging approaches like IVM show particular promise for PCOS by circumventing ovarian stimulation altogether. The selection of ART modality must be individualized based on infertility duration, previous treatment failures, ovarian reserve parameters, and comprehensive risk assessment, with particular attention to optimizing outcomes while minimizing the characteristic risks associated with PCOS pathophysiology.

ART can be considered after failed ovulation induction treatment with high pregnancy rates per cycle, especially in younger women. So IVF should be considered after other ovulation induction therapies. However, conception and delivery are highly valued by healthcare professionals and women with PCOS and even when cost and risks are increased, some may elect to undertake IVF.

6. Conclusion(s)

This chapter has systematically reviewed the current evidence-based strategies for polycystic ovary syndrome (PCOS), emphasizing a lifespan, multi-phenotype management model that addresses the heterogeneous needs of affected individuals across fertility and nonfertility dysfunctions. The cornerstone of PCOS management remains lifestyle intervention, tailored to individual preferences, adherence, and phenotypic presentations. Dietary modifications, physical activity, and behavioral support have demonstrated efficacy in improving metabolic parameters, ovulatory function, and quality of life, though challenges persist in long-term sustainability and accessibility.

For pharmacological and surgical interventions, the chapter highlighted targeted approaches for specific clinical features and lifecycle stages. Anti-obesity agents

(e.g., GLP-1 receptor agonists and orlistat) and insulin-sensitizing therapies (e.g., metformin and inositol) show promise in addressing metabolic dysregulation, while fertility-focused treatments (e.g., letrozole and clomiphene) remain first-line for anovulatory infertility. Special attention was given to vulnerable populations, such as adolescents and pregnant women, where treatment decisions should balance benefits against potential risks, necessitating shared decision-making with patients and guardians.

Looking ahead, the paradigm shift toward patient-centered care demands further integration of multidisciplinary strategies. Emerging research should prioritize personalized medicine, leveraging genetic, hormonal, and lifestyle data to refine treatment algorithms to specific PCOS subtypes. The role of digital health tools (e.g., mobile apps for lifestyle tracking) and community-based interventions warrants exploration to enhance adherence and scalability. Additionally, longitudinal studies are needed to evaluate the safety and efficacy of novel therapies, particularly in underrepresented groups.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 9

The Role of Bariatric Surgery in the Treatment of Obese Women with Polycystic Ovary Syndrome

Esra Söylemez

Abstract

PCOS, or polycystic ovary syndrome, is a frequently diagnosed hormonal condition in females, distinguished by disrupted ovulation, excess androgen production, and multiple cysts in the ovaries. Obesity frequently accompanies PCOS, worsening insulin resistance, menstrual irregularities, fertility challenges, and other metabolic abnormalities. Therefore, controlling body weight is a crucial aspect of PCOS management. This chapter examines the therapeutic potential of bariatric surgery in managing polycystic ovary syndrome in female patients, particularly those with morbid obesity, based on the most recent clinical studies and guidelines. Bariatric procedures not only promote weight loss but also improve ovarian function by restoring ovulation, reducing insulin resistance, lowering androgen levels, and enhancing fertility outcomes. Furthermore, these hormonal changes after surgery are associated with improved life satisfaction and a decreased likelihood of developing chronic cardiovascular and metabolic diseases. The content includes patient eligibility criteria for bariatric surgery, comprehensive pre-surgical evaluation, common procedural techniques like sleeve gastrectomy and Roux-en-Y gastric bypass, and postoperative care protocols. It also discusses the importance of monitoring fertility, managing pregnancies, and ensuring long-term follow-up with a multidisciplinary approach. In conclusion, when carefully selected and managed, obesity surgery procedures provide a secure and efficient treatment alternative for addressing both metabolic and reproductive issues in women with PCOS. A personalized, multidisciplinary care plan is essential to achieve the best results.

Keywords: PCOS, androgens, obesity, bariatric surgery, AMH

1. Introduction

Polycystic ovary syndrome (PCOS) is a multifactorial and persistent endocrine disorder impacting roughly 6–15% of women during their reproductive lifespan [1]. This syndrome is characterized by heightened androgen presence, disrupted ovulation, and the identification of polycystic ovarian features, often occurring alongside obesity. The coexistence of obesity exacerbates the clinical features of PCOS and amplifies its metabolic complications [2]. When standard interventions such as

lifestyle modification and pharmacological treatments fall short, bariatric surgery has emerged as an increasingly favored therapeutic option.

Surgical eligibility for bariatric procedures typically includes individuals with a body mass index (BMI) of 40 kg/m^2 or higher, or those with a BMI of 35 kg/m^2 accompanied by obesity-related health conditions such as PCOS [3]. In women with PCOS, weight loss resulting from bariatric surgery has been linked to marked improvements in hormonal regulation and metabolic health. Postoperative findings often reveal reductions in androgen levels, normalization of menstrual cycles, reestablishment of ovulatory function, and an increased likelihood of spontaneous pregnancy—all indicative of restored endocrine balance [4]. A fundamental driver of these benefits is the improvement in insulin sensitivity, which reduces excessive ovarian androgen production that was initially stimulated by hyperinsulinemia.

From a metabolic viewpoint, bariatric surgery enhances insulin responsiveness, lowers fasting glucose and HbA1c levels, and induces positive changes in lipid profiles and cardiovascular risk markers [5]. Many aspects of the metabolic syndrome commonly observed in PCOS patients, including impaired glucose tolerance and dyslipidemia, tend to regress after surgery, delivering both immediate and long-term health advantages.

In addition to physiological benefits, bariatric surgery provides psychological and social improvements. Many women with PCOS experience mood disorders, anxiety, and dissatisfaction with their body image, which frequently improve following surgical weight loss [6]. For women of reproductive age, enhanced fertility potential and the regularization of menstrual cycles contribute significantly to a better quality of life.

Despite this, recognizing the necessity for patient-specific treatment plans is fundamental. PCOS presents with considerable heterogeneity, and not all patients are suitable candidates for surgical intervention. A thorough preoperative evaluation conducted by a cross-functional team—including specialists in endocrinology, gynecology, surgery, nutrition, and mental health—is essential. Moreover, long-term postoperative follow-up is vital for maintaining treatment benefits and managing potential complications.

In conclusion, bariatric surgery shows considerable potential in improving both hormonal and metabolic impairments observed in obese females diagnosed with PCOS. However, it should be integrated within a personalized, multidisciplinary care framework. Further extended randomized clinical trials are necessary to solidify the evidence, refine patient selection, and clarify the function of bariatric procedures in reproductive endocrinology and obesity treatment.

2. Pathophysiological relationship between PCOS and obesity

PCOS represents a heterogeneous endocrine disorder distinguished by elevated levels of androgens, persistent anovulation, and polycystic ovarian morphology. The coexistence of obesity in women with PCOS significantly worsens both reproductive dysfunctions and metabolic abnormalities. Estimates suggest that 40–80% of women diagnosed with PCOS are overweight or obese, which intensifies the clinical severity of the syndrome [7].

A central pathophysiological feature of PCOS is insulin resistance, a condition strongly associated with obesity. Excess visceral adiposity triggers the release of free fatty acids and pro-inflammatory cytokines such as tumor necrosis factor-alpha

(TNF-α) and interleukin-6 (IL-6), which interfere with normal insulin signaling pathways [8]. This state of hyperinsulinemia potentiates luteinizing hormone (LH) effects on theca cells in the ovaries, resulting in increased androgen synthesis [9]. Concurrently, elevated insulin decreases liver synthesis of sex hormone-binding globulin (SHBG), raising circulating free testosterone levels. These hormonal disruptions manifest clinically as hirsutism, acne, and ovulatory disturbances [10].

Adipose tissue acts both as an energy depot and as a dynamic endocrine organ. In obesity, adipokines such as leptin and resistin are elevated, whereas levels of adiponectin—which promotes insulin sensitivity—are decreased [11]. These alterations aggravate systemic insulin resistance. Despite high leptin levels, central leptin resistance impairs appetite control and energy homeostasis. Moreover, the pro-inflammatory environment created by adipose tissue negatively affects ovarian function, further disturbing ovulation [12].

In obese individuals, changes in hypothalamic gonadotropin-releasing hormone (GnRH) pulsation frequency contribute to an amplified LH to follicle-stimulating hormone (FSH) ratio, stimulating excess androgen production by the ovaries. This hormonal imbalance is frequently observed in PCOS and is worsened by obesity. Additionally, increased visceral fat promotes aromatization of androgen precursors to estrogens, resulting in hyperestrogenism, which raises the risk of endometrial hyperplasia and infertility [13].

Inflammation linked to obesity is another critical factor that exacerbates PCOS. Elevated cytokines, including IL-6, C-reactive protein (CRP), and monocyte chemoattractant protein-1 (MCP-1), contribute to the chronic low-intensity inflammation characteristic of PCOS. This inflammation impairs ovarian function and insulin signaling, further complicating the clinical profile [14]. Oxidative stress also plays a role by promoting endothelial dysfunction, atherosclerosis, and increased cardiometabolic risk, thereby raising morbidity in affected women.

Genetic and epigenetic factors are implicated in the interplay between PCOS and obesity. Variants in genes such as FTO and MC4R have been associated with susceptibility to both conditions [15]. Furthermore, maternal obesity during gestation may induce epigenetic modifications affecting fetal ovarian development, potentially elevating the offspring's risk for PCOS.

Obesity and PCOS are interlinked through a multifaceted, reciprocal relationship. Obesity amplifies the metabolic and endocrine abnormalities characteristic of PCOS, including insulin resistance, hyperandrogenism, and ovulatory dysfunction. Hence, targeting obesity is a fundamental aspect of PCOS management. Achieving long-term control of PCOS requires a holistic, multidisciplinary approach aimed at restoring hormonal equilibrium and optimizing body composition.

3. Limitations of conventional treatment methods in PCOS

Polycystic ovary syndrome (PCOS) stands as one of the most common endocrine disorders impacting women during their reproductive years, characterized by anovulation, elevated androgen levels, and metabolic irregularities [1]. The traditional management of this multifactorial syndrome mainly involves pharmacological interventions combined with lifestyle modifications aimed at symptom control. However, the durability of these treatments and their ability to cater to individualized patient needs remain controversial. Below is a summary of the major challenges associated with these conventional therapies.

Conventional approaches focus largely on symptom management: oral contraceptives are employed to regulate menstrual cycles, anti-androgen medications are used to reduce manifestations like hirsutism and acne, and ovulation stimulants such as clomiphene citrate or letrozole are utilized to tackle infertility [16]. Despite these benefits, these treatments do not fundamentally address the underlying drivers of PCOS, including insulin resistance and persistent low-grade inflammation. Consequently, symptom relief is often temporary, and relapse commonly occurs following cessation of therapy [17].

Metformin is frequently prescribed to improve insulin sensitivity, particularly in PCOS patients with impaired glucose metabolism [18]. Nevertheless, the evidence regarding its effectiveness in enhancing ovulatory function and pregnancy rates is mixed, with many studies showing only modest improvements [19]. Additionally, gastrointestinal side effects linked to metformin frequently reduce patient compliance, which limits its overall efficacy.

Clomiphene citrate remains the first-line ovulation induction agent; however, about 20–25% of women with PCOS experience resistance, failing to achieve ovulation despite treatment [20]. Aromatase inhibitors like letrozole serve as alternative options, yet their long-term safety profile remains inadequately established. Moreover, these agents carry risks such as multiple gestations and ovarian hyperstimulation syndrome (OHSS), which raise clinical concerns [21].

Obesity aggravates both hormonal and metabolic aspects of PCOS, making lifestyle interventions including diet and exercise fundamental to therapy [22]. Despite this, sustained weight loss is challenging for most patients, often resulting in only short-term benefits. Even when weight is successfully reduced, improvements in key symptoms such as ovulatory irregularities and hirsutism may be modest or inconsistent [23].

Psychological issues such as anxiety, depression, and poor body image are commonly seen in women with PCOS [24]. Unfortunately, psychological support is frequently neglected in routine management, which can reduce motivation and adherence to treatment plans. Without addressing mental health needs, long-term outcomes and patient satisfaction may suffer.

Given the heterogeneity of PCOS phenotypes, uniform treatment protocols are unlikely to be effective for all individuals. However, conventional management often relies on standardized algorithms that do not fully accommodate individual differences, especially in patients presenting with infertility or pronounced metabolic dysfunction. Tailored therapeutic strategies are therefore essential to optimize patient outcomes [25].

In conclusion, while conventional treatments may offer temporary symptom control in PCOS, they fall short in targeting the fundamental pathophysiological mechanisms in the long run. Due to the complex interplay of insulin resistance, inflammation, psychological factors, and phenotypic diversity, there is a growing need for comprehensive and personalized approaches. Emerging options such as metabolic surgery warrant consideration and highlight the necessity to revisit current treatment paradigms in PCOS care.

4. Bariatric surgery: definition, indications and types

4.1 Definition

Bariatric surgery refers to a spectrum of surgical strategies aimed at achieving long-term weight reduction in individuals with obesity. These operations function

through restrictive mechanisms (limiting food intake), malabsorptive processes (impairing nutrient absorption), or a combination of both modalities [26]. Evidence from recent literature indicates that such procedures not only support weight loss but also play a crucial role in modulating endocrine functions, including the enhancement of insulin sensitivity and amelioration of metabolic syndrome components [27].

4.2 Indications

The eligibility criteria for bariatric surgery are outlined in clinical guidelines established by the American Society for Metabolic and Bariatric Surgery (ASMBS) and the National Institutes of Health (NIH) [28]. These include:

- An individual with a BMI of 40 kg/m^2 or higher, regardless of the existence of other medical conditions.
- A BMI threshold of 35 kg/m^2 in the context of substantial comorbid conditions like type 2 diabetes, hypertension, obstructive sleep apnea, or lipid metabolism disorders.
- A BMI within the range of 30–34.9 kg/m^2 in conjunction with severe and treatment-resistant metabolic abnormalities is increasingly considered an indication for metabolic surgical intervention, particularly in the management of type 2 diabetes.

In women diagnosed with polycystic ovary syndrome (PCOS), bariatric surgery is gaining recognition as a viable treatment option when conventional therapies—such as dietary regulation, exercise, and pharmacologic agents—fail to yield satisfactory outcomes [29].

4.3 Types of surgery

Bariatric interventions are generally classified based on their physiological mechanism and the degree of anatomical modification involved. Each procedure has unique indications, advantages, and potential risks. Technological progress has increasingly favored minimally invasive methods, including laparoscopic and endoscopic techniques, which are associated with faster recovery and reduced complication rates.

4.3.1 Conventional surgical approaches

1. Roux-en-Y gastric bypass (RYGB)

   Procedure overview: This technique integrates both restrictive and malabsorptive elements by creating a small gastric pouch connected to the distal portion of the jejunum, thereby bypassing a segment of the small intestine responsible for nutrient absorption [30].
   Clinical outcomes: RYGB consistently results in substantial and sustained weight loss, typically in the range of 60–70%, and is associated with significant remission rates for comorbidities such as type 2 diabetes, hypertension, and dyslipidemia [31].

Potential Complications: Risks may include dumping syndrome, anastomotic strictures, internal herniation, nutritional deficiencies, and peptic ulcers.

2. Sleeve gastrectomy

Procedure overview: This restrictive method entails the surgical removal of 75–80% of the stomach, leaving a slender, tubular gastric remnant [32].
Clinical outcomes: Outcomes are generally comparable to RYGB, with a sustained weight loss of 50–60%. Notably, the resection of the gastric fundus—an area rich in ghrelin-producing cells—helps suppress appetite [33].
Potential complications: These may include staple line leaks, strictures, and the development or exacerbation of gastroesophageal reflux disease (GERD).

3. Biliopancreatic diversion with duodenal switch (BPD/DS)

Procedure overview: BPD/DS is the most extensive and complex bariatric surgery, incorporating both restrictive and malabsorptive components. It includes sleeve gastrectomy followed by a rerouting of the distal ileum to the duodenum, effectively bypassing a large portion of the small intestine [34].
Clinical outcomes: This method provides the most dramatic weight loss outcomes (typically 70–80%) and offers high remission rates for severe metabolic conditions. Due to its complexity, It is generally considered appropriate for patients classified as extremely obese, with a body mass index greater than 50 kg/m^2.
Potential complications: Among the principal risks are inadequate protein and calorie intake, malabsorption of lipophilic vitamins, and various gastrointestinal side effects.

4.3.2 Minimally invasive bariatric techniques

These techniques are increasingly employed due to their lower morbidity and faster recovery profiles and can be grouped into three major categories:

1. Endoscopic bariatric therapies

These interventions offer weight loss benefits without major anatomical alterations:
Endoscopic sleeve gastroplasty (ESG): Utilizes endoscopic suturing to reduce stomach volume, thereby inducing restriction. Typically suitable for patients with a BMI between 30 and 40 kg/m^2 [35].
Duodenal mucosal ablation (DMA): This involves targeted thermal ablation of the proximal duodenal mucosa to improve glucose metabolism and is currently considered a promising non-surgical therapy for type 2 diabetes [36].
Transoral gastric bypass: An experimental procedure under clinical evaluation, designed to mimic the physiological effects of RYGB.

2. Intragastric balloon systems

These involve the temporary placement of an air- or fluid-filled balloon within the stomach to promote early satiety and caloric restriction.

Endoscopic balloons: Inserted via endoscopy and typically removed after 6–12 months.
Swallowable balloons (e.g., Elipse): These are ingested orally, expand in the stomach, and naturally pass through the digestive tract after deflation [37].

3. Laparoscopic surgical techniques

Laparoscopy offers significant advantages over open surgery, including reduced hospital stays and fewer complications:
Laparoscopic sleeve gastrectomy (LSG): This technique entails the laparoscopic removal of nearly 75% of the stomach, performed via minimally invasive abdominal incisions.
Laparoscopic adjustable gastric banding (LAGB): The technique entails the application of a silicone band near the gastric fundus to construct a reduced-capacity pouch. Due to its relatively low long-term success rate, its use has declined.

Clinical efficacy of minimally invasive techniques depends heavily on patient adherence to postoperative protocols and metabolic response. For instance, ESG typically results in 15–20% weight loss within 1 year [38], whereas intragastric balloons may induce a 10–15% reduction in body weight [39]. Complication rates are generally lower than those of conventional surgery, with common side effects including nausea, vomiting, cramping, and transient dyspepsia. Serious complications—such as bleeding, mucosal damage, or perforation—are rare.

Minimally invasive bariatric techniques offer a significant option for patients unsuitable for conventional surgery or those opting for non-surgical interventions. When applied within a comprehensive multidisciplinary care framework and combined with sustainable lifestyle changes, these interventions can produce durable improvements in weight and metabolic health. Continued innovation in this field is expected to expand their clinical utility and long-term effectiveness.

In conclusion, bariatric surgery remains a cornerstone in the clinical management of obesity and its accompanying metabolic dysfunctions. Optimal outcomes rely on individualized treatment planning, careful procedural selection, and extended multidisciplinary monitoring over an extended period.

5. Effects of bariatric surgery in PCOS

Polycystic ovary syndrome (PCOS) represents one of the most commonly encountered endocrine abnormalities in women of reproductive age, marked by hyperandrogenism, oligo/anovulation, and the presence of polycystic ovarian morphology. Obesity is not only a contributing factor to the development of PCOS but also exacerbates its reproductive and metabolic sequelae [40]. In recent years, bariatric surgery has emerged as a potential treatment modality for addressing complications associated with PCOS, beyond its established role in treating morbid obesity.

Surgical weight loss interventions have been shown to modulate key aspects of PCOS pathophysiology, particularly by improving insulin sensitivity and enhancing glucose regulation [41]. Procedures such as sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) significantly lower HbA1c, fasting insulin concentrations, and HOMA-IR indices, indicating better glycemic control [42]. These benefits are evident not only in patients with impaired glucose tolerance but also in insulin-resistant women with PCOS.

Another notable endocrine effect of bariatric surgery is the reduction in hyperandrogenemia. Postoperative assessments frequently demonstrate a marked decline in total and free testosterone levels [43]. Concurrently, there is a rise in sex hormone-binding globulin (SHBG), which further reduces the bioavailability of androgens present in the bloodstream. Post-surgical outcomes commonly involve a significant alleviation of hyperandrogenic features such as hirsutism, acneiform eruptions, and androgen-dependent hair thinning.

Restoration of ovulatory function is another significant benefit observed in PCOS patients after bariatric surgery. Many women report spontaneous resumption of ovulatory menstrual cycles, often within the first year postoperatively [44]. Studies have documented that up to 80% of women may experience the normalization of menstrual patterns within 6–12 months [45].

This improvement in reproductive endocrinology leads to enhanced fertility outcomes, particularly among women with PCOS-related infertility. Increased rates of spontaneous conception have been noted in patients undergoing SG and RYGB [46]. Nonetheless, clinical guidelines recommend delaying pregnancy for 12–18 months after surgery to allow for weight stabilization and to minimize the risk of adverse outcomes associated with rapid weight loss and potential micronutrient deficiencies during early gestation [47].

In addition to physical symptoms, PCOS imposes substantial psychological and social burdens. Obesity, infertility, and hyperandrogenic features often contribute to diminished self-esteem, depression, and anxiety. Bariatric surgery has been linked to improved psychological well-being, largely through weight normalization and the resolution of hormonal imbalances [48]. Enhancements in body image and mood are commonly reported, contributing to a better overall overall well-being.

The therapeutic success of bariatric procedures in PCOS management is optimized through structured postoperative care and multidisciplinary follow-up. Ongoing assessment by a collaborative team—including dietitians, endocrinologists, gynecologists, and mental health professionals—is essential. This approach ensures the early identification and management of nutritional deficiencies, hormonal fluctuations, and reproductive health considerations.

In summary, bariatric surgery offers multifaceted benefits for obese women with PCOS, not only by facilitating significant and prolonged decrease in body mass but also by improving metabolic control, reproductive function, and psychosocial health. For patients who do not respond adequately to conventional therapies, surgical intervention may serve as a valuable and effective treatment modality. However, individualized assessment and long-term multidisciplinary care remain critical to achieving favorable outcomes.

6. Risks and follow-up of bariatric surgery

While bariatric surgery is acknowledged as a highly effective intervention for the management of high-grade obesity and its associated comorbidities, it is not without significant risks. As with all surgical procedures, the potential for complications necessitates a comprehensive and multidisciplinary approach that encompasses both preoperative preparation and sustained postoperative care [49].

Early postoperative complications, typically occurring within 1 month after surgery, can include serious and potentially life-threatening events. These may consist of hemorrhage, anastomotic leakage, infections, deep vein thrombosis (DVT), and pulmonary

embolism. Among these, anastomotic leaks are particularly critical and often present during the initial postoperative week, requiring prompt detection and urgent surgical or interventional management [50]. Mortality rates after bariatric procedures generally range between 0.1 and 0.3%, although outcomes are closely tied to the expertise of the surgical team and the quality standards of the healthcare institution [51].

Late complications tend to manifest months or even years after surgery and are more frequently observed following procedures with a malabsorptive component. Common issues include macro- and micronutrient deficiencies—especially involving iron, vitamin B12, vitamin D, calcium, and folate—along with conditions such as dumping syndrome, small bowel obstructions, cholelithiasis, and internal hernias [52]. For instance, Roux-en-Y gastric bypass (RYGB) is particularly concomitant with iron and vitamin B12 deficiencies, which may contribute to the development of anemia. Additionally, long-term skeletal complications such as reduced bone mineral density and secondary hyperparathyroidism have been identified [53].

Beyond physical complications, psychological and behavioral concerns are also notable in the postoperative period. Patients may encounter challenges such as altered body image, recurrence of disordered eating patterns, depression, anxiety, or even substance use disorders. Some studies have reported a slight elevation in suicide risk following bariatric surgery, highlighting the critical role of preoperative psychological evaluation and continued mental health support [54].

The success of bariatric interventions extends far beyond the surgical procedure itself. Long-term efficacy is closely linked to diligent follow-up protocols. During the first postoperative year, subsequent clinical assessments are commonly planned at intervals of 1, 3, 6, and 12 months, transitioning to annual evaluations thereafter. These evaluations focus on monitoring key indicators, including body weight, BMI, glycemic control, lipid profiles, hepatic function, bone density, nutritional markers, and mental health status.

A multidisciplinary follow-up strategy—involving bariatric surgeons, endocrinologists, nutritionists, mental health professionals, and physical therapists—is essential to address the diverse and evolving needs of patients throughout their recovery and adaptation process [49, 53].

Particular attention is warranted for women of childbearing age. Clinical guidelines advise postponing conception for 12–18 months post-surgery to facilitate weight stabilization and dietary optimization. During this window, individualized nutrition plans and supplementation regimens are imperative to prevent micronutrient deficits. In addition, preconception counseling and coordinated obstetric care are vital for ensuring favorable maternal and fetal outcomes [52].

In conclusion, although surgical intervention yields considerable improvements in weight loss outcomes and overall health improvement for individuals with severe obesity, its potential complications—both early and late—underscore the necessity of structured, multidisciplinary postoperative management. Continued refinement of follow-up protocols through long-term, high-quality randomized controlled trials will be essential to improve patient safety and long-term success.

7. Clinical practice guidelines and recommendations

In obese individuals with polycystic ovary syndrome (PCOS) who are being considered for bariatric surgery, clinical decision-making should be guided by a comprehensive, multidisciplinary evaluation. The assessment ideally involves collaboration

among an endocrinologist, gynecologist, bariatric surgeon, clinical dietitian, and mental health professional to ensure holistic care planning.

7.1 International guidelines

Joint recommendations by the American Association of Clinical Endocrinologists (AACE), the American Society for Metabolic and Bariatric Surgery (ASMBS), and The Obesity Society (TOS) provide clear criteria for patient selection for metabolic surgery [55]. Bariatric intervention is advised in the following scenarios:

- Individuals with a Body Mass Index (BMI) $\geq$ 40 kg/m^2, regardless of comorbidities
- Patients exhibiting a body mass index of 35 kg/m^2 or higher, accompanied by comorbidities including type 2 diabetes mellitus, hypertension, dyslipidemia, or obstructive sleep apnea
- Selected individuals with a BMI ranging from 30 to 34.9 kg/m^2, particularly those with poorly controlled metabolic disorder clusters despite conventional therapy, pending approval by a multidisciplinary team

The Endocrine Society also highlights bariatric surgery as a viable therapeutic option in women with PCOS and morbid obesity, emphasizing its role in improving ovulatory function, reducing hyperandrogenism, and enhancing insulin sensitivity [56]. Weight loss, achieved through surgical means, is recognized as a key mechanism in restoring reproductive and metabolic health in these patients.

7.2 Choice of surgical method and PCOS-specific considerations

Among the commonly employed techniques, laparoscopic sleeve gastrectomy (LSG) is preferred due to its technical simplicity, relatively lower risk of complications, and marked efficacy in promoting weight reduction. Additionally, SG contributes to marked decreases in systemic androgen concentrations, offering specific advantages for affected individuals with PCOS. Roux-en-Y Gastric Bypass (RYGB), on the other hand, is especially beneficial for patients requiring strict glycemic control, such as those with concurrent type II diabetes mellitus.

The choice of surgical technique in females diagnosed with PCOS should be individualized and informed by multiple factors, including the severity of ovulatory dysfunction, plans for future fertility, degree of insulin resistance and systemic inflammation, and the occurrence of coexisting conditions such as sleep apnea or cardiovascular risk factors.

Given the reproductive concerns in many women with PCOS, extensive malabsorptive procedures are generally avoided due to the potential impact on nutrient absorption. In such contexts, sleeve gastrectomy offers a safer and effective alternative with fewer nutritional risks [57].

Emerging minimally invasive treatments, such as the endoscopic intragastric balloon (EIB), are gaining clinical interest. This non-surgical approach has demonstrated efficacy in promoting weight reduction, improving hormonal profiles, and normalizing menstrual patterns in obese women with PCOS [58, 59]. Compared to surgical interventions, EIB offers a more gradual and conservative weight loss trajectory, with the added benefits of being cost-effective and reversible.

Selecting the most appropriate bariatric intervention for women with PCOS requires careful clinical judgment and a patient-specific approach. While laparoscopic sleeve gastrectomy remains a commonly favored option due to its efficacy and safety profile, the endoscopic intragastric balloon represents a promising alternative, particularly in patients seeking less invasive solutions. Ultimately, long-term success relies on aligning surgical strategy with individual reproductive goals, comorbidity profiles, and risk tolerance, guided by a collaborative and multidisciplinary framework.

8. Conclusion and future perspectives

Bariatric surgery demonstrates encouraging benefits in the short and intermediate term for women affected by PCOS; however, evidence regarding its long-term effects remains scarce. A large proportion of current studies rely on observational data, often limited by small cohorts and brief follow-up durations, which hinders the ability to draw definitive conclusions. Accordingly, there is a pressing requirement for randomized controlled studies of prospective design, incorporating prolonged follow-up, to comprehensively evaluate the durability of the procedure's outcomes and potential relapse.

Furthermore, investigating the differential impact of bariatric surgery across various PCOS phenotypes could enhance the development of tailored therapeutic approaches. Specifically, comparing outcomes between phenotypes characterized predominantly by insulin resistance and those marked by ovulatory dysfunction is essential to improve patient stratification and maximize treatment success.

In addition, more in-depth studies on the effects of weight-loss surgery on reproductive parameters are warranted. Robust clinical data are necessary to clarify the ideal timing for conception after surgery, to identify potential metabolic complications during gestation, and to evaluate perinatal health.

In summary, bariatric surgery represents a comprehensive intervention for obese women with PCOS, leading to significant improvements in metabolic parameters, hormonal regulation, ovulation, fertility, and overall quality of life. Nonetheless, this approach requires careful consideration within a multidisciplinary context, tailored to the individual patient's profile. Future rigorous and well-structured investigations will be pivotal in elucidating the long-term outcomes associated with bariatric procedures and in informing evidence-based clinical guidelines.

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Chapter 10

Use of Myoinositol in PCOS

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Abstract

Polycystic ovary syndrome (PCOS) is a prevalent and complex endocrine disorder that affects women of reproductive age. It is primarily characterized by metabolic disturbances, notably insulin resistance (IR), hyperandrogenism, and ovulatory dysfunction, often leading to menstrual irregularities and fertility challenges. Myoinositol (MI), a naturally occurring carbocyclic sugar alcohol, has gained significant attention as a promising therapeutic agent for PCOS due to its crucial role as a second messenger in insulin signal transduction. This chapter reviews the current understanding of PCOS pathophysiology and explores the multifaceted applications of myoinositol in its management. Evidence from numerous randomized controlled trials and meta-analyses suggests that MI supplementation can improve insulin sensitivity, reduce hyperinsulinemia, ameliorate hormonal imbalances by lowering androgen levels and normalizing the luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio, restore menstrual regularity, and enhance oocyte quality and reproductive outcomes. Comparisons with metformin indicate comparable efficacy for several parameters, often with a superior tolerability profile for MI. Furthermore, combination therapies, particularly MI with D-chiro-inositol in a physiological ratio (e.g., 40:1), and MI with other agents like alpha-lactalbumin or folic acid, are discussed for their potential synergistic effects. While clinical guidelines are increasingly recognizing MI as a viable option, particularly for improving menstrual cycles and as an alternative to metformin, a clear understanding of the evidence, patient preferences, and the need for further high-quality research remains paramount for individualized patient care.

Keywords: polycystic ovary syndrome (PCOS), myoinositol (MI), insulin resistance, D-chiro-inositol (DCI), metformin, hormonal imbalance, ovulatory dysfunction, infertility, combination therapy

1. Introduction

Polycystic ovary syndrome (PCOS) is widely acknowledged as a highly prevalent and intricate endocrine condition that impacts women of reproductive age globally [1]. Due to its varied nature, PCOS presents with a wide array of clinical characteristics. Such variability can complicate diagnosis, highlighting the importance of accurately ruling out other endocrine disorders with comparable presentations [2]. Key characteristics of the syndrome usually involve a mix of hormonal disturbances,

notably hyperandrogenism (increased androgen levels), ovulatory issues leading to irregular or missed periods, and the typical polycystic ovarian morphology (PCOM) identified *via* ultrasound [3].

The health consequences associated with PCOS extend significantly beyond reproductive issues. They include substantial metabolic disturbances such as insulin resistance (IR), an increased risk of developing type 2 diabetes mellitus (T2DM), dyslipidemia, and heightened cardiovascular disease (CVD) risk [4]. Furthermore, PCOS is linked to an elevated risk for specific malignancies, most notably endometrial cancer [5], and can profoundly affect psychological health, contributing to increased rates of anxiety and depression among affected individuals [6]. The intricate nature and multi-system impact of PCOS highlight the critical need for a comprehensive understanding and effective management strategies.

Insulin resistance has emerged as a fundamental component in the pathophysiology of PCOS, affecting a significant majority of individuals with the syndrome, often independent of body weight [7, 8]. This metabolic dysfunction is intricately linked with hyperandrogenism, establishing a complex interplay that drives many of the syndrome's clinical manifestations [9]. Recognizing the central role of insulin resistance, therapeutic strategies aimed at improving insulin sensitivity have gained prominence. Within this context, myoinositol (MI), a naturally occurring isomer belonging to the vitamin B complex family, has attracted considerable research interest [10]. Myoinositol functions as an intracellular secondary messenger critical for insulin signal transduction and glucose metabolism [11]. Accumulating evidence suggests that disruptions in inositol metabolism might contribute to the insulin resistance observed in PCOS, thereby positioning MI as a potential therapeutic agent capable of addressing this core pathophysiological mechanism [12].

2. Definition and prevalence of PCOS

Formally, PCOS is described as an intricate endocrine condition marked by a collection of signs and symptoms mainly caused by excess androgens and impaired ovulation [13]. It stands as the predominant endocrine disorder impacting women in their reproductive years globally [14]. Diagnosis typically adheres to the Rotterdam criteria, which were internationally endorsed and established in 2003 by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) [15]. Based on these guidelines, PCOS is diagnosed if a minimum of two of these three characteristics are observed (once other potential endocrine conditions are excluded): [1] oligo-ovulation or anovulation (evidenced by irregular or absent menstrual cycles); [2] clinical indicators (like hirsutism, acne, or alopecia) and/or biochemical proof (raised androgen levels) of hyperandrogenism; and [3] polycystic ovarian morphology identified on ultrasound, characterized by 20 or more follicles in at least one ovary, or an ovarian volume of 10 mL or more [16].

PCOS prevalence varies significantly depending on the diagnostic criteria used and the specific population studied. Worldwide, estimates generally fall between 4 and 20% for women of reproductive age [17]. Research employing the Rotterdam criteria tends to show higher prevalence numbers (often reported as 11.9 to 17.8%) than studies using the more stringent 1990 National Institutes of Health (NIH) criteria, which require both hyperandrogenism and chronic anovulation for a diagnosis [18]. Moreover, prevalence rates seem to vary among different ethnic backgrounds. Systematic analyses indicate potentially lower prevalence in Chinese women (around

5.6% with Rotterdam criteria) and Caucasian women (approximately 5.5% with NIH criteria), contrasting with potentially higher rates in Black women (about 6.1% with NIH criteria) and Middle Eastern populations (with a wide range of 6.1–16.0% based on the criteria applied) [19].

Despite its high frequency, a substantial number of women affected by PCOS, up to 70%, remain undiagnosed in the community [20]. This significant diagnostic gap highlights the inherent challenges presented by the syndrome's clinical heterogeneity and may reflect insufficient awareness or inconsistent screening practices within healthcare systems [18]. An apparent increase in PCOS prevalence, particularly noted within adolescent populations, further emphasizes its growing public health importance [21].

2.1 Clinical manifestation

The clinical manifestations are typically grouped into reproductive, dermatological (related to hyperandrogenism), metabolic, and psychological categories.

Reproductive manifestations: Irregular menstrual cycles are a defining feature for many women with PCOS. Oligomenorrhea (infrequent menstruation, typically cycles >35 days) or amenorrhea (absence of menstruation for ≥3 months) results from chronic oligo- or anovulation [22]. Consequently, PCOS represents a major cause of infertility due to ovulatory dysfunction [23]. Additionally, women with PCOS face increased risks of pregnancy complications, including higher rates of miscarriage (estimated at 30–50%) [24].

Dermatological Manifestations (Hyperandrogenism): Clinical evidence of excess androgen action is frequent. Common manifestations include hirsutism (excess terminal hair growth in a male-like pattern on the face, chest, abdomen, or back), persistent acne vulgaris (often resistant to standard treatments), and androgenic alopecia (thinning hair or hair loss, typically in a male pattern distribution) [25]. Another potential sign is acanthosis nigricans, characterized by dark, thickened, velvety skin, usually found in body creases like the neck or axillae, which strongly suggests underlying insulin resistance [26].

Metabolic Manifestations: Metabolic dysfunction is a prominent aspect of PCOS. IR is considered a fundamental characteristic, estimated to affect 50–70% of women with PCOS, occurring in both obese and lean [27]. This often leads to compensatory hyperinsulinemia, observed in approximately 80% of obese women with PCOS and 30–40% of their lean counterparts [28]. Obesity, especially abdominal or central adiposity, is common, affecting roughly 40–80% of women with the syndrome [29].

Psychological Manifestations: PCOS is associated with a significant psychological burden. Affected women report higher rates of anxiety and depressive symptoms compared to women without the condition [6]. Factors such as the visible symptoms of hyperandrogenism, challenges with weight management, infertility concerns, and the long-term health risks contribute to a diminished health-related quality of life [30].

2.2 Etiology

The etiology of PCOS is complex and remains incompletely defined. It is broadly accepted as a multifactorial disorder resulting from the intricate interplay of genetic susceptibility and various environmental factors. A single definitive cause accounting for the full spectrum of the syndrome has not been identified [31].

Genetic Factors: Evidence strongly supports a significant genetic contribution to PCOS, with heritability estimates ranging up to 79% [32]. Familial aggregation studies consistently show that first-degree female relatives of women with PCOS have a substantially higher risk (20–40%) of developing the syndrome themselves [33]. Genome-wide association studies (GWAS) have successfully identified numerous genetic loci associated with increased PCOS risk, although these known variants currently explain only a minor proportion (approximately 10%) of the overall heritability [34]. Research is increasingly focusing on the role of epigenetic modifications, such as alterations in DNA methylation patterns or microRNA expression profiles, which can be influenced by both the intrauterine environment and postnatal factors, potentially mediating gene-environment interactions in PCOS development [35].

Environmental and Lifestyle Factors: A range of environmental factors and lifestyle choices are implicated in the pathogenesis and manifestation of PCOS. The intrauterine environment is considered critical, with evidence suggesting that fetal exposure to excess androgens or elevated anti-Müllerian hormone (AMH) may program developmental pathways predisposing individuals to PCOS later in life [36, 37]. Exposure to certain environmental endocrine-disrupting chemicals (EDCs), such as bisphenol A (BPA), is another area of investigation [38]. Postnatally, lifestyle factors exert a profound influence. Unhealthy dietary patterns, sedentary behavior, and consequent weight gain or obesity are well-established contributors that can unmask or significantly worsen the clinical and metabolic features of PCOS in genetically susceptible individuals [39].

Pathophysiological Mechanisms: The pathophysiology of PCOS is characterized by several interconnected mechanisms. Hyperinsulinemia directly stimulates androgen production by ovarian theca cells and possibly the adrenal glands [40]. It may also contribute to hyperandrogenism indirectly by suppressing the liver's production of sex hormone-binding globulin (SHBG), thereby increasing the levels of biologically active free androgens [41]. Intrinsic ovarian dysfunction, including abnormal steroidogenesis and arrested follicular development, is also key [42]. Neuroendocrine disturbances play a role, often involving altered gonadotropin-releasing hormone (GnRH) pulsatility, leading to disproportionately high luteinizing hormone (LH) secretion relative to follicle-stimulating hormone (FSH) levels, which further promotes ovarian androgen synthesis and impairs follicle maturation [43].

2.3 Introduction to myoinositol

Myoinositol (MI) is a naturally occurring carbocyclic sugar alcohol, specifically one of the nine stereoisomers of inositol. It is ubiquitously present in the human body and obtained through dietary intake as well as endogenous synthesis, primarily in the kidneys [44]. MI serves as a fundamental structural component of cell membranes and acts as an important precursor for the synthesis of various inositol phosphates and phosphoinositides [45]. These derivatives, particularly phosphatidylinositol phosphates, function as essential second messengers in numerous intracellular signaling cascades, including those regulating cell growth, differentiation, and metabolic processes [46]. Of particular importance is the role of MI-derived inositol phosphoglycans (IPGs) in mediating the post-receptor effects of insulin, thereby influencing glucose uptake and metabolism [47].

The growing interest in myoinositol within the context of polycystic ovary syndrome arises principally from its recognized insulin-sensitizing properties [11]. Emerging research indicates that women with PCOS may exhibit alterations in

inositol metabolism, potentially leading to a relative deficiency of MI or its downstream mediators like IPGs within insulin-sensitive tissues [48].

By potentially correcting defects in insulin signal transduction, myoinositol supplementation aims to ameliorate the state of insulin resistance and reduce the compensatory hyperinsulinemia characteristic of PCOS. The following section will elaborate on the specific biochemical and physiological mechanisms by which myoinositol is thought to exert these therapeutic effects in women with PCOS.

3. Clinical evidence for myoinositol in PCOS management

3.1 Insulin sensitivity and glucose metabolism

Multiple randomized controlled trials (RCTs) have assessed MI's benefits on insulin sensitivity in PCOS patients. In a meta-analysis in 2017 by Unfer, V. et al., 490 PCOS women from 9 RCTs were evaluated. The results demonstrated that after 12–24 weeks of treatment with MI supplementation (2–4 g/day), fasting insulin levels were reduced($P = 0.009$), and a reduction in HOMA-IR ($P = 0.041$) was observed compared to placebo [49].

In another systematic review conducted by Greff et al., 26 RCTs with 1691 PCOS patients were analyzed, and the same results on reduction of fasting insulin level and HOMA-IR after treatment with MI were observed. Still, no significant difference was seen between the inositol and the metformin [50].

Furthermore, in a systematic review by Fitz et al., 30 trials with 2230 patients were included and assessed the role of myoinositol or D-chiro-inositol (DCI) for metabolic parameters. MI has fewer gastrointestinal side effects than metformin, but it may not be superior to metformin [51].

The evidence from studies indicates that MI supplementation is comparable to metformin and can enhance insulin sensitivity. MI's role in the phosphoinositide 3-kinase (PI3K) pathway can result in these effects, and by facilitating glucose transporter type 4 (GLUT4) activity, glucose uptake can be increased in peripheral tissues like skeletal muscle and adipose tissue [51].

3.2 Hormonal imbalance

Hormonal dysregulation is another feature of PCOS, characterized by elevated androgen levels and an imbalanced LH to FSH ratio, which may cause symptoms like hirsutism, acne, and ovulatory dysfunction.

In different RCTs and meta-analyses, MIs have been shown to reduce androgen levels and normalize gonadotropin secretion. In earlier studies and RCTs, the benefits of inositol on the hormonal profile of individuals with PCOS were established, and the administration of 2–4 mg MI for 12 weeks or 6 months, according to different RCTs, has shown improvement in hirsutism score and reduction in the androgen levels, FSH, LH, and LDL cholesterol [52–54].

These effects result from MI's insulin-sensitizing properties, which by downregulating cytochrome P450c17α enzyme activity can affect ovarian theca cell androgen production [48].

In a 2023 systematic review by Greff et al., 26 randomized controlled trials involving 1691 participants were evaluated. As shown, inositol can reduce total and free testosterone levels, as well as androstenedione levels, elevate SHBG levels, and

regularize menstrual cycles. These effects were comparable to metformin, but the side effects were fewer [50].

Unfer et al. in 2017 in a meta-analysis of 9 RCTs found that MI (2–4 g/day) may cause a reduction of testosterone concentration in comparison to control groups ($P = 0.099$), but without change in androstenedione levels. SHBG can be increased significantly after 24 weeks of treatment with MI ($P = 0.026$) [49].

Another meta-analysis of 17 RCTs, which consisted of 1083 PCOS patients, showed that MI has positive effects on androstenedione and prolactin levels. However, other endocrine parameters, including LH, FSH, estradiol, SHBG, dehydroepiandrosterone, and total testosterone levels, were not affected [55].

In a 2024 systematic review conducted for the updated international PCOS guidelines, it was emphasized that although MI appears to have effects in improving hyperandrogenism and metabolic parameters, higher-quality research and more trials are necessary to strengthen the evidence [51].

MI enhances aromatase activity, facilitating the conversion of androgens into estrogens, thereby supporting dominant follicle selection and reducing total androgen levels. Additionally, MI stimulates hepatic production of sex hormone-binding globulin (SHBG), which attaches to free androgens, effectively lowering their bioavailability [54].

3.3 Ovulation and menstrual regularity

In a 2003 double-blinded RCT involving 283 PCOS patients, Gerli et al. found significant improvements in the luteal phase and ovulation rate in the inositol group (100 mg, twice a day) compared to a placebo, along with significant weight loss in the inositol group [56].

A 2018 meta-analysis of 10 RCTs, evaluating 601 women with PCOS diagnosis in three groups of inositol, metformin, and placebo, found that inositol had a beneficial influence on ovulation rate and increased the frequency of menstrual cycles [57].

Another review by Tanbo et al. in 2018 emphasized that the myoinositol (2 g) and chiro-inositol (0.6 g), when taken twice per day, and for a duration of 2–6 months, according to studies, can increase the likelihood of spontaneous ovulation compared to the placebo [58].

It was shown in the studies that an excess of inositol in the ovary increases FSH sensitivity and can also improve fertilization rates and embryo quality in PCOS patients [59].

3.4 Reproductive outcomes

An important challenge for PCO patients is infertility due to anovulation or poor oocyte quality. MI enhances fertility outcomes—both in spontaneous conception and assisted reproductive technologies (ART)—by improving ovulation, oocyte maturation, and embryo quality. Clinical evidence from RCTs and meta-analyses demonstrates MI's efficacy as a natural adjunct.

In a meta-analysis that included 7 RCTs in 2018, 360 PCOS patients undergoing ART were observed. The results showed that MI supplementation (2–4 g/day) increased clinical pregnancy rates by 66% ($P = 0.001$) and improved oocyte quality compared to controls, and also, gonadotropin requirements were reduced by about

20% [60]. An RCT from 2015 with 60 PCOS patients candidates for *in vitro* fertilization (IVF) showed that MI (4 g/day) for 12 weeks boosted the number of mature oocytes by 30% and raised implantation rates by 18% versus placebo, and also higher fertilization rates were observed [61]. MI's enhance follicular fluid dynamics and reduce oxidative stress, which optimizes the ovarian microenvironment for oocyte development.

For spontaneous conception, a 2013 RCT with 92 PCOS women reported that a combination of MI (2 g/day) and folic acid for 6 months increased live birth rates by 22% over placebo, and 68% of treated women achieved spontaneous ovulation and subsequent pregnancies [49].

Systematic reviews emphasize MI's role in improving ovulation and oocyte quality; it is also safe and has synergy with fertility protocols [50]. MI supports mitochondrial function in oocytes and reduces follicular arrest, and so has fertility-enhancing effects both in natural conception and ART settings [62].

3.5 Metabolic parameters

Metabolic syndrome is a group of metabolic disturbances that can significantly elevate the risk of heart disease and type 2 diabetes. These conditions include insulin resistance, abdominal obesity, high blood pressure, and dyslipidemia [63].

These features can be consequences of metabolic dysregulation in PCOS. Studies show the efficacy of MI for addressing these metabolic abnormalities. Myoinositol supplementation can lower fasting insulin levels, facilitate glucose uptake, and reduce hyperinsulinemia through intracellular insulin signaling pathways [64].

Greff et al. in the study of 26 RCTs (2023) reported that MI can better normalize menstrual cycles and is also associated with BMI and weight reduction compared with placebo, but non-inferiority in most outcomes compared to metformin [50].

Salehpour et al. in 2016 evaluated the impact of MI on metabolic and cardiovascular health in women older than 30 years with PCOS. Over 3 months, 50 participants received MI plus folic acid, and the researchers evaluated metabolic markers before and after treatment. Results demonstrated significant improvements in insulin sensitivity, reductions in cholesterol, LDL, homocysteine, and blood pressure. The findings suggest that MI supplementation may help normalize metabolic profiles and reduce cardiovascular risks in older PCOS patients [65].

However, in the meta-analysis examined by Fitz et al. in 2024, the authors believe that the evidence supporting inositol's role in PCOS management remains limited and requires further studies [51].

MI is also important in the prevention of Gestational Diabetes by its insulin-sensitizing effects, but the effects on fetal macrosomia and neonatal hypoglycemia were not seen [66, 67].

3.6 Comparison with metformin

Metformin is an important and effective drug in the management of PCOS, particularly for its insulin-sensitizing potential [68]. However, as highlighted in several systematic reviews and meta-analyses, MI is a natural alternative whose efficacy is comparable to metformin and has lower side effects.

Kutenaei et al. conducted a systematic review and meta-analysis comparing myoinositol (MI) and metformin across nine studies, involving 331 patients treated

with metformin and 307 patients treated with MI. Their findings indicated that both treatments effectively improved insulin sensitivity, ovulation rates, and hormonal balance in PCOS patients. The study indicated that myoinositol (MI) may serve as a viable alternative to conventional drug therapies for PCOS patients [69].

In a meta-analysis of Greff et al. in 2023, inositol showed non-inferiority in most outcomes, such as normalizing menstrual cycles and improving metabolic parameters, compared to metformin; however, with fewer gastrointestinal adverse effects, such as bloating, nausea, and generalized weakness [50]. In another meta-analysis of 8 RCTs and 1088 PCOS patients comparing MI and metformin in assessing hormonal and metabolic parameters in women with PCOS, it was demonstrated that both drugs are equally beneficial without any significant difference [70].

A meta-analysis in 2024 on 30 RCTs and 2230 patients showed that metformin may improve waist-hip ratio and hirsutism more effectively than inositol; however, it likely has no advantage in reproductive outcomes, and the evidence remains uncertain about its impact on BMI. Myoinositol is associated with fewer gastrointestinal adverse effects [51]. In another RCT, by Ravn et al., the efficacy of MI and metformin (MI 4 g/day or MET 2 g/day.) was compared in 45 women with PCOS. The result showed that both treatments effectively reduced HOMA-IR values; however, MI had fewer gastrointestinal side effects than metformin, suggesting better tolerability [71].

Myoinositol's role in enhancing oocyte quality and embryo development in ART is assessed in different studies and discussed before; however, its effect on reducing the likelihood of OHSS has not been approved in comparison to metformin [72].

In a meta-analysis by Lijun Lin in 2024, 20 RCTs involving 1827 patients reported that both metformin and MI may reduce the risk of OHSS in PCOS patients. However, no significant improvement in pregnancy outcomes was seen. Metformin is more effective in the agonist protocol for lowering OHSS risk by reducing E2 levels on the day of trigger, and it also has a good effect on the number of mature oocytes. At the same time, myoinositol may shorten the duration of gonadotropin use. However, further RCTs are necessary to confirm the findings [73].

Both MI and metformin are effective in managing PCOS, and the choice between them often depends on individual patient preferences, tolerability, and specific clinical scenarios.

3.7 Mental health and mood regulation

PCOS is often accompanied by psychological challenges, like anxiety, depression, and mood swings, which are closely linked to the hormonal and metabolic disturbances [74]. Studies demonstrate that MI has benefits for both emotional and mental health.

The mechanism by which MI can affect is its role in insulin signaling, neurotransmitter activity, and cellular stability. It supports cell signaling through pathways involving phosphoinositides and inositol glycans, affecting metabolism and brain function. Inositol modulates serotonin pathways, so it can reduce symptoms of depression, panic disorder, and OCD. Its safety and effectiveness can make it an alternative to SSRIs for some patients [75].

A 2013 systematic review and meta-analysis by Mukai et al. found that inositol may provide therapeutic benefits for individuals with depression, particularly those with PMDD [76].

4. Dosage and administration of myoinositol in PCOS treatment

4.1 Standard dosage and duration of treatment

As studied in multiple articles and meta-analyses, the best dosage of myoinositol for PCOS management is '2 grams twice daily', and the total dose is '4 grams per day', which can affect insulin sensitivity and glucose metabolism, hormonal balance, and ovulatory function. According to different studies, it is recommended that a '3 to 6 months' treatment is necessary to achieve the best results [77, 78].

4.2 Myoinositol and D-chiro-inositol ratio in supplements

MI is converted into D-chiro-inositol (DCI) *via* the action of the epimerase enzyme, which is insulin-dependent. In healthy women, ratio of MYO/DCI in the plasma is approximately 40:1, while in ovarian follicular fluid, it reaches 100:1. However, in patients with PCOS patients, this ratio becomes inverted and can go as low as 0.2:1. So it seems the '40:1 ratio' of myoinositol to D-chiro-inositol is optimal according to its physiological concentrations and clinical evidence for best performance [79, 80].

4.3 General safety profile and adverse effects

According to medical research and clinical evidence, myoinositol is a safe product. MI has lower side effects in comparison to other agents like metformin. As we know, metformin is associated with gastrointestinal adverse effects such as nausea, diarrhea, and abdominal discomfort that are not tolerated by some consumers. However, more common adverse effects of MI are mild gastrointestinal discomfort, including nausea, flatulence, and diarrhea, which are rare and typically transient [81]. MI is also a safe product in patients with metabolic comorbidities since it has no impact on liver or kidney function [51]. These side effects of MI are typically dose-dependent (higher doses of myoinositol may lead to increased gastrointestinal discomfort) and occur more frequently at higher dosages exceeding 12 grams per day. For standard dosages (4 grams per day), side effects are rare and generally resolve without intervention [82].

5. Myoinositol in combination therapies for PCOS

Combination of MI with other supplements to synergize its effect may be a good choice due to its potential therapeutic effects. There are Many products based on inositol, and different combinations of myoinositol and other supplements have been formulated over the years [78].

5.1 Myoinositol and D-chiro-inositol combination

D-Chiro-Inositol is a natural isomer of inositol. Insulin stimulates the conversion of MI into DCI *via* the epimerase enzyme. MI facilitates cellular glucose uptake by inducing GLUT4 translocation to the cell membrane, inhibits adenylate cyclase activity, and reduces the release of free fatty acids from adipose tissue, so MI has a role in

glucose catabolism. DCI takes part in glycogen synthesis [44, 63]. Both MI and DCI can mimic insulin and consequently lower postprandial blood glucose [83].

MI also stimulates FSH signaling, while DCI can act as an aromatase inhibitor and is responsible for insulin-mediated androgen synthesis [84]. So, they both have benefits in terms of hormonal balance and metabolic disturbance in PCOS. According to the results of different studies, the MI and DCI combination has good benefits in all aspects of PCOS, which include improving insulin sensitivity, decreasing blood pressure, TG, TChol concentrations, and also BMI. They can also reduce serum androgen concentrations and increase SHBG. Their effectiveness in improving the menstrual cycle and ovulation rate was also studied in different studies [84–87]. Although MI alone shows positive results, the use of DCI alone is still controversial due to insufficient evidence. The best MYO/DCI ratio is when used in 40:1 [79, 84]. Studies suggest that lowering this ratio (e.g., 20:1, 10:1, or lower) is ineffective and may even diminish treatment efficacy, whereas increasing the MYO ratio appears to enhance therapeutic outcome. More studies in different ratios, such as 100:1, are required [80].

5.2 Myoinositol and metformin

Metformin is an antidiabetic drug that is effective in the management of PCOS, as established by multiple studies. It can lower glucose synthesis directly or indirectly by affecting the liver, and acts on the gut to enhance glucose utilization and stimulate glucagon-like peptide 1 (GLP-1) production. Metformin acts on a molecular level and can inhibit the mitochondrial respiratory chain in the liver and also reduce the expression of gluconeogenic enzymes, so it can improve insulin sensitivity and have a good effect on fat metabolism without a direct effect on pancreatic insulin production [68, 88]. The combined use of inositol and metformin has been proposed to provide therapeutic benefits for individuals with PCOS. In a double-blinded RCT in 2023, two groups of PCOS were studied in metformin (500 mg) and metformin (500 mg) plus inositol groups for 6 months. The author suggests that combining inositol and metformin significantly impacts menstrual cycle length and also improves hormonal and biochemical parameters. So they will have a synergistic effect [89]. In another systematic review and meta-analysis of 35 studies, the effectiveness of inositol, metformin, and their combination was evaluated. The results show the effectiveness of such treatments in clinical pregnancy rate, live birth rate, and the risk of OHSS in PCOS individuals candidates for ART [90].

MI and metformin in combination have a synergistic effect. While metformin is commonly associated with gastrointestinal adverse effects, the addition of myo-inositol has been shown to mitigate these adverse effects, improving overall patient compliance. This combination can also reduce HOMA-IR after 3 months of treatment [91]. Combination treatment can also improve menstrual cycles, BMI, acne score, and hormonal parameters, and is associated with better ovulatory and reproductive outcomes [84, 91].

5.3 Combination with folic acid

Folic acid plays a crucial role in DNA synthesis, red blood cell production, and fetal development during pregnancy. Folic acid also supports cellular health, elevates folate concentration in follicular fluid, decreases the concentration of homocysteine, and positively affects oocyte and embryo quality. So, the combination of MI and folic acid works synergistically to improve metabolic and reproductive outcomes,

especially in PCOS [92, 93]. Adding '200 micrograms of folic acid' per dose to inositol enhances its therapeutic effects according to studies [84, 93, 94]. This combination is available in different forms, like oral tablets, capsules, and powders.

5.4 Myoinositol and oral contraceptives combination

Oral contraceptives (OCPs) are frequently prescribed to regulate menstrual cycles and manage hyperandrogenism in women with PCOS. Although it is effective in androgen-related symptoms such as acne and hirsutism, OCPs can exacerbate insulin resistance and lipid parameters (increasing cholesterol and triglyceride levels). Simultaneously, they can lower serum levels of FSH, LH, and SHBG. The main mechanism of OCP is the suppression of FSH, which therefore reduces the endometrial cancer in the future. The combination of myoinositol with OCPs offers a promising strategy to mitigate these adverse effects while enhancing therapeutic outcomes [91, 95].

After 12 months of treatment, combination therapy with MI and OCPs has a greater impact on endocrine, metabolic, and clinical profiles in patients with PCOS compared to OCPs alone, although it does not significantly affect BMI [95, 96]. It was shown that treatment with OCP alone may increase weight, while MI + OCP together did not change patients' weight and BMI [84]. In an article published in 2021, the effect of combination therapy was evaluated in teenagers. The results showed improvements in weight and BMI parameters, and also an effective improvement in metabolic parameters. This strategy could avoid or postpone pharmacological therapy during adolescence. It also has a good effect on lifestyle [97].

5.5 Myoinositol and alpha-lactalbumin

Alpha-lactalbumin (α-LA) is a whey protein. It can be presented in mammalian milk (about 20–25% of whey and 22% of proteins in human milk) naturally. Because of α-LA's low immunogenicity, it is a safe alternative for individuals who have allergies. As α-LA contains essential amino acids such as tryptophan, lysine, and branched-chain amino acids and bioactive peptides, it can have antibacterial, anti-inflammatory, prebiotic, and immunomodulatory effects. α-LA significantly enhances the intestinal absorption of vital compounds like vitamins and minerals (e.g., vitamin D and iron). It is also processed by pancreatic enzymes into bioactive peptides that result in different biological activities, such as growth stimulation and immune system modulation. Additionally, α-LA has been studied for its impact on neurological functions and may have good effects on sleep, mood disorders, depression, and even cancer [98–101].

Its role in PCOS management is because α-LA promotes the secretion of glucagon-like peptide 2 (GLP-2), which upregulates the expression of SGLT-1 and GLUT-2 transporters, thereby improving the intestinal absorption of inositols. So the combination of inositol and α-LA has potentially good effects in PCOS management, even in inositol-resistant cases [102, 103].

Oliva et al. studied the effects of MI in combination with α-LA in myoinositol-resistant PCOS women were evaluated. Resistant PCOS patients who received 2gr MI without any response in 3 months were again treated with the 2gr MI in combination with 50 mg α-LA twice a day, for an additional 3 months. The results demonstrated a rise in MI plasma levels compared to baseline; also, an improvement in hormone and lipid profiles was seen [104]. In another review article by Pandya et al., emphasis

is placed on the effectiveness of α-LA on intestinal absorption of inositols, as well as improving gut dysbiosis, inflammation, and insulin resistance, and therefore improvement in metabolic and hormonal profile and ovulation rate in PCOS [105]. Kamenov et al. also showed that combination therapy with 2 g of MI and 50 mg of α-LA, compared to MI alone, has benefits on ovulation rate, menstrual cycle duration, reduction in BMI, and improvement of hyperandrogenism [106].

5.6 Other combination therapies and lifestyle modification

A large number of studies on the effect of alpha lipoic acid and MI or DCI in PCOS management are available. Alpha lipoic acid is an antioxidant and an enzymatic cofactor of the mitochondrial respiratory chain. Both MI and ALA activate GLUT-4, which is crucial for glucose uptake and supporting carbohydrate metabolism. So the combination of MI and ALA can potentially improve metabolic and hormonal profiles and reproductive outcomes in PCOS patients, especially in individuals with insulin resistance [84, 107].

Vitamin D deficiency is responsible for some abnormalities in PCOS, like menstrual irregularities and fertility issues. Additionally, research highlights the positive impact of vitamin D on hormonal balance in PCOS patients, influencing testosterone, LH, FSH, and AMH levels [108, 109]. Several studies demonstrated the efficacy of this supplement, especially in combination with inositol, in improving metabolic parameters and fertility outcomes [110]. In a systematic review by Katyal et al. in 2024 to assess the efficacy of inositol and vitamin D in fertility outcomes and metabolic parameters among PCOS patients, the authors showed that these supplements are a potentially beneficial option [111]. In a study evaluating the effectiveness of vitamin D plus myoinositol, folic acid, and melatonin compared to the groups that did not receive vitamin, the positive effect of combination therapy on IVF outcomes was established [112].

Other combinations of MI with different supplements like L-carnitines, L-arginine, L-cysteine, magnesium, selenium, ZINC, etc., are available, and also some of them showed improvements in metabolic and hormonal parameters, but wider studies to achieve the best combination ratio and doses are necessary [113, 114].

Lifestyle interventions, including diet and exercise in accompany with MI supplementation, can enhance metabolic and hormonal responses [115].

While combination therapies are beneficial, several factors must be considered: First is Individualization. Treatment should be based on a patient's tolerance, specific phenotype, metabolic profile, and reproductive goals to obtain the best response. Second, the safety of products. Although studies did not show any significant side effects in combination therapies, careful monitoring is often necessary. At least further studies are required for optimal dosing regimens and evaluation of the long-term efficacy of these combinations.

6. Current medical guidelines and recommendations for myoinositol use in PCOS

The stance of major clinical guidelines on inositol use in PCOS has evolved cautiously. The 2018 International Evidence-based Guideline initially classified inositol as an experimental therapy, advising against its routine use due to insufficient high-quality evidence for clinical efficacy, particularly for fertility outcomes [116].

However, the 2023 update of this International Guideline [117], alongside the 2025 Society of Obstetricians and Gynecologists of Canada (SOGC) Position Statement [118], reflects a nuanced shift. Informed by recent systematic reviews, these guidelines now suggest that inositol (primarily MI) could be considered for women with PCOS. This remains a conditional recommendation, based on generally low-quality evidence, emphasizing the importance of shared decision-making that incorporates individual patient preferences and values, acknowledging the limited potential for harm but also the uncertain clinical benefits for many outcomes. The SOGC statement specifically suggests MI supplementation can be used as an alternative to metformin

Recommendation	Guideline Source	Strength of Recommendation	Quality of Evidence
For women with PCOS, any form of inositol may be an option, guided by patient preference, given its low risk of harm and potential for metabolic enhancement, though clinical benefits are currently restricted	International CPG, 2023	Conditional	Low
Inositol is a possible consideration for individuals with PCOS, citing its low harm potential and some evidence suggesting benefits for metabolic function and menstrual cycle	SOGC, 2025	Conditional	Low
MI supplementation may be utilized to enhance menstrual regularity and address anovulation in PCOS, serving as an alternative to metformin, contingent on patient preferences and tolerability of side effects	SOGC, 2025	Weak	Moderate
Currently, inositol (any form) for treating PCOS-related infertility is classified as experimental. Emerging efficacy data underscores the necessity for additional research	International CPG, 2018	Conditional (Against Use)	Low
Healthcare practitioners are advised to inquire about patients' use of supplements, including inositol, for managing their PCOS	SOGC, 2025	Strong	High
Practitioners should inform patients that inositol's regulation differs from prescription medications, and robust evidence might be constrained by study limitations (e.g., sample size, design, and dosage variations)	SOGC, 2025	Strong	High
Ensuring women can access impartial, evidence-based information, while acknowledging and respecting individual patient choices, is a duty of policy makers and healthcare	International CPG, 2023	Practice Point	N/A
Patients utilizing inositol or other complementary treatments should be prompted to discuss this use with their healthcare professional	International CPG, 2023	Practice Point	N/A
Due to a lack of high-quality evidence, specific formulations, dosages, or combinations of inositol cannot be definitively endorsed at this time	International CPG, 2023	Practice Point	N/A

Table 1.
Summary of clinical practice guidelines recommendations for MI use.

for improving menstrual cycle regularity and anovulation, citing moderate-certainty evidence for comparable efficacy but better tolerability [118].

These updated recommendations are grounded in systematic reviews synthesizing data from numerous, often small and methodologically limited, randomized controlled trials (RCTs). Evidence regarding metabolic benefits is mixed; some analyses show potential improvements in certain markers (like triglycerides or SHBG) with MI or DCI compared to placebo or metformin, while others find metformin superior for parameters like fasting insulin or waist-hip ratio. Robust evidence supporting significant improvements in live birth rates or overall clinical pregnancy rates with inositol remains lacking. Hormonal effects are similarly inconsistent across studies. A key finding, however, is the consistent observation that MI is generally well-tolerated and correlates with significantly lower gastrointestinal side effects than metformin. The overall quality of evidence across most outcomes is frequently downgraded due to risk of bias, small sample sizes, heterogeneity, and imprecision, underpinning the cautious and conditional nature of current recommendations.

In practice, current guidelines advise that healthcare providers should proactively inquire about supplement use, including inositol, and counsel patients appropriately. This counseling should include information about the regulatory status of inositols (often classified as natural health products or supplements, not drugs), the limitations of the existing scientific evidence regarding efficacy for many clinical outcomes, the lack of robust long-term safety data, and the potential variability in product quality and dosage. While research often investigates 4 grams of MI daily, sometimes in combination with DCI (often in a 40:1 ratio), guidelines emphasize that there is currently insufficient evidence to strongly recommend any specific type, dose, or combination of inositols. The decision to use MI should therefore be individualized, focusing on patient priorities (e.g., preference for avoiding metformin side effects when addressing cycle irregularity) and a clear understanding of the evidence gaps. The summary of clinical practice guideline (CPG) recommendations is provided in **Table 1**.

7. Conclusion

Myoinositol has emerged as a significant and promising therapeutic agent in the multifaceted management of PCOS. Its primary mechanism of action, centered on enhancing insulin sensitivity *via* its role as a precursor to inositol phosphoglycans, directly addresses a core pathophysiological defect in a majority of women with PCOS. The extensive body of clinical evidence, including numerous RCTs and systematic reviews, supports the efficacy of MI (typically at doses of 2–4 grams per day) in improving key metabolic parameters such as fasting insulin and HOMA-IR, correcting hormonal dysregulations including hyperandrogenism and elevated LH/FSH ratios, and promoting reproductive health by restoring ovulation, improving oocyte quality, and increasing pregnancy rates.

A notable advantage of myoinositol is its excellent safety profile and tolerability, particularly when compared to metformin, with which it demonstrates comparable benefits for several outcomes, such as menstrual cycle regulation, but often with fewer gastrointestinal side effects. The combination of MI with D-chiro-inositol, especially in the physiological 40:1 ratio, has shown particular promise in leveraging the distinct roles of these isomers in glucose metabolism and steroidogenesis. Other combination therapies, such as with folic acid or alpha-lactalbumin, may further

enhance therapeutic efficacy or improve MI bioavailability, especially in individuals who may exhibit inositol resistance.

Current international clinical guidelines have evolved to conditionally recommend inositol for women with PCOS, particularly for improving menstrual regularity and as an alternative to metformin, emphasizing the importance of shared decision-making based on individual patient needs and preferences. However, it is acknowledged that the quality of evidence for some outcomes varies, and further high-quality, large-scale, long-term studies are still warranted to definitively establish optimal dosing regimens, long-term benefits and safety, and its role across the diverse spectrum of PCOS phenotypes.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 11

Lycopene: A New Hope for PCOS Management

Minahil Haq, Sarmad Bashir Mian, Parveen Abbas, Muhammad Umar, Sadia Khan and Saima Naz

Abstract

Polycystic ovarian syndrome (PCOS) remains one of the most common endocrine disorders among women of reproductive age, with particularly high prevalence in South Asian populations. While conventional therapies such as metformin and antioxidant supplements (including myo-inositol, vitamin D, and folic acid) offer some relief, the search for more effective, accessible options continues. Lycopene—a naturally occurring carotenoid best known for its presence in tomatoes—has gained attention for its remarkable antioxidant capacity, estimated to be nearly 100 times stronger than vitamin E. This chapter examines lycopene's therapeutic potential in PCOS management. Experimental evidence suggests lycopene plays a protective role in improving histomorphological, endocrine, and metabolic disturbances by combating oxidative stress, regulating inflammatory pathways, and restoring hormonal balance. It acts through mechanisms such as inhibition of the IGF-1 receptor signaling and reduction of reactive oxygen species, both of which are key contributors to PCOS pathology. Additionally, its lipophilic nature allows for efficient absorption and distribution, especially from processed sources like tomato paste. Given its wide availability, affordability, and broad therapeutic profile, lycopene emerges as a promising natural compound that could complement existing treatment strategies and offer new hope for women living with PCOS.

Keywords: lycopene, polycystic ovarian syndrome (PCOS), antioxidants, insulin resistance, metabolic disorders, oxidative stress/reactive oxygen species ROS

1. Introduction

"Polycystic ovarian syndrome (PCOS) is one of the commonest endocrine disorders in females, affecting 4–18% of women of reproductive age group. The prevalence of PCOS is quite high in South Asian women, especially in Pakistani women [1]. "In Pakistan, PCOS is also common among unmarried women" [2].

The etiology of PCOS remains multifactorial, involving complex interactions between genetic susceptibility, environmental influences, and lifestyle features. Insulin resistance, present in approximately 70–80% of PCOS patients, serves as a key pathophysiological driver, creating a vicious cycle of hyperinsulinemia, hyperandrogenism, and metabolic dysfunction. The syndrome's heterogeneous presentation

often leads to delayed diagnosis and suboptimal management, with many women experiencing symptoms for years before receiving appropriate medical attention.

Environmental factors, including dietary patterns, physical inactivity, and exposure to endocrine-disrupting chemicals, contribute significantly to PCOS development and progression. The rising prevalence of PCOS in developing countries correlates with urbanization, westernization of diets, and sedentary lifestyles. These epidemiological trends highlight the importance of preventive strategies and early intervention approaches that address modifiable risk factors.

Many antioxidants are tried along with metformin in the treatment of PCOS, which includes myo-inositol, vitamin D biotin, and folic acid. The therapeutic landscape for PCOS has evolved considerably, yet significant gaps remain in addressing the underlying pathophysiology. Current treatment modalities often target individual symptoms rather than the multisystem nature of the disorder. Hormonal contraceptives, although effective for menstrual regulation and hyperandrogenism, do not address metabolic dysfunction or long-term complications. Metformin, despite its insulin-sensitizing effects, shows variable efficacy and may cause gastrointestinal side effects that limit patient compliance.

The search for novel therapeutic approaches has intensified due to the limitations of conventional treatments and the growing understanding of PCOS as a complex endocrine-metabolic disorder. Natural compounds with multiple mechanisms of action offer particular promise, as they can simultaneously target oxidative stress, inflammation, and metabolic dysfunction without the side effect profiles associated with synthetic drugs.

"After using them for 12 weeks, there was a significant improvement in symptoms, such as acne, hirsutism, and weight gain" [3]. "Antioxidant micronutrient intake—particularly vitamin E, zinc, selenium, chromium, and carotenoid—was quite lower in women with PCOS who also had metabolic syndrome" [4]. "Lycopene represents a potent antioxidant demonstrating singlet oxygen quenching capacity approximately" [1]. More than 200 articles have been published on the health benefits of lycopene. It proved its beneficial effects in various carcinomas (prostrate, ovarian, and renal cell), atherosclerosis, human papillomavirus, cataracts, asthma, liver diseases, kidney ischemia, and neurotoxic disorders [5]. It is approachable for all groups of socioeconomic status.

2. Pathogenesis and treatment of PCOS

PCOS stems from genetic, environmental, and lifestyle factors, with key issues including:

i. High androgen levels from ovaries and adrenals disrupt ovulation, causing irregular periods and hirsutism.

ii. Affects 50–70% of patients, increasing androgens and reducing SHBG, worsening symptoms.

iii. High ROS and inflammatory markers like TNF-α harm ovarian and metabolic function.

iv. High LH-to-FSH ratio drives androgen excess, impairing ovulation.

Current treatments focus on symptom relief:

i. 5–10% weight loss can restore ovulation and improve insulin sensitivity.

ii. Oral contraceptives regulate cycles, metformin addresses insulin resistance, and clomiphene aids fertility.

iii. Antioxidants such as myo-inositol, vitamin D, and lycopene (a potent antioxidant) show promise in reducing oxidative stress.

3. Structure and properties of lycopene

Lycopene (C40H56) was initially revealed from tomatoes by Millardet in 1876 and subsequently named by Schunck [6]. Currently, it is ubiquitous in human dietary consumption worldwide due to its powerful antioxidant properties [7]. It is a member of the beta-carotenoid group, vibrant red in color. In plants, algae, and photosynthetic organisms, lycopene mediates yellow, orange, and red pigmentation while facilitating photosynthesis and photoprotection. The desaturation and isomerization steps, catalyzed by specific enzymes, lead to the formation of the fully conjugated lycopene molecule. This biosynthetic pathway is highly regulated by environmental conditions, including temperature, light intensity, and nutrient availability, which explains the variability in lycopene content among different plant sources and growing conditions.

The evolutionary significance of lycopene extends beyond its antioxidant properties, as it serves critical roles in photosynthesis and photoprotection in plant systems. The compound's ability to absorb light in the blue-green spectrum and dissipate excess energy as heat protects photosynthetic apparatus from photodamage. This photoprotective function translates into similar protective mechanisms in human tissues, particularly against UV-induced oxidative damage.

3.1 The physicochemical properties

> *"Lycopene is a vibrant red carotenoid with a molecular weight of 536.89 g/mol, comprising 89.45% carbon and 10.51% hydrogen. This unsaturated acyclic carotenoid contains 11 linear conjugated and 2 non-conjugated double bonds. Lycopene demonstrates optimal stability at pH 3.5–4.5, with a log P value of 17.64, rendering it water-insoluble [6].*

The high lipophilicity of lycopene necessitates special considerations for formulation and delivery in therapeutic applications. Conventional aqueous-based delivery systems show poor lycopene solubility and stability, leading to reduced bioavailability and therapeutic efficacy. Advanced delivery technologies, including liposomal encapsulation, nanoemulsions, and cyclodextrin complexation, have been developed to overcome these limitations and enhance lycopene's therapeutic potential.

Temperature sensitivity represents another critical factor affecting lycopene stability and biological activity. While moderate heating can enhance lycopene release from cellular matrices and improve bioavailability, excessive heat exposure leads to isomerization and degradation. The optimal processing temperature range of 60–80°C maximizes lycopene extraction while minimizing thermal damage. This

temperature dependency has important implications for food preparation methods and supplement manufacturing processes.

Light exposure, particularly UV radiation, rapidly degrades lycopene through photoisomerization and oxidation reactions. This photosensitivity necessitates protective packaging and storage conditions for lycopene-containing products. The degradation products formed during light exposure may possess different biological activities or potentially harmful properties, emphasizing the importance of proper handling and storage protocols.

3.2 Structure of lycopene

The molecular structure of lycopene is characterized by its unique arrangement of conjugated double bonds, as illustrated in **Figure 1**. This structural configuration is responsible for its exceptional antioxidant properties and vibrant red coloration [6].

Commercially available lycopene can be produced by chemical synthesis, fermentation, or isolation from a small number of abundant natural sources, such as biosynthesis from algae, fungi, and plants, and, at a smaller scale, by microorganisms. "While tomatoes represent the primary dietary source of lycopene, content varies significantly due to environmental factors, agricultural practices, cultivar selection, and ripening stage. Lycopene is also present in the seeds and peel residues of various fruits and vegetables, including watermelon, apricot, papaya, guava, red grapes, pink grapefruit, pumpkins, rosehip, fig, orange, mango, pomegranate, and carrot" [5, 8].

Seasonal variations significantly impact lycopene concentrations in natural sources, with peak levels typically observed during optimal growing conditions. Climate factors such as temperature fluctuations, rainfall patterns, and soil composition influence plant metabolism and carotenoid synthesis. These natural variations can result in 2- to 3-fold differences in lycopene content between seasons, highlighting the importance of standardized extraction methods and quality control measures for therapeutic applications.

Post-harvest handling practices also influence lycopene retention and quality. Storage temperature, humidity levels, and packaging methods affect the rate of lycopene degradation and conversion between isomeric forms. Controlled atmosphere storage and modified atmosphere packaging have been developed to maintain lycopene stability during transportation and retail distribution.

The lycopene content varies significantly across different tomato-based products and forms. As demonstrated in **Figure 2**, processed tomato products generally contain higher concentrations of lycopene compared to fresh tomatoes, with tomato powder showing the highest levels.

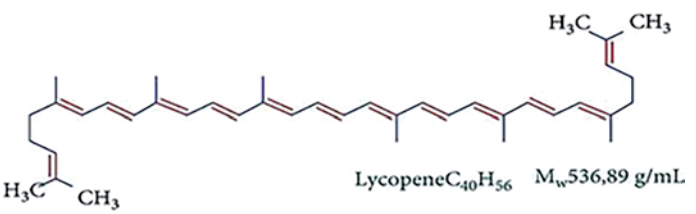

Figure 1.
Molecular structure of lycopene.

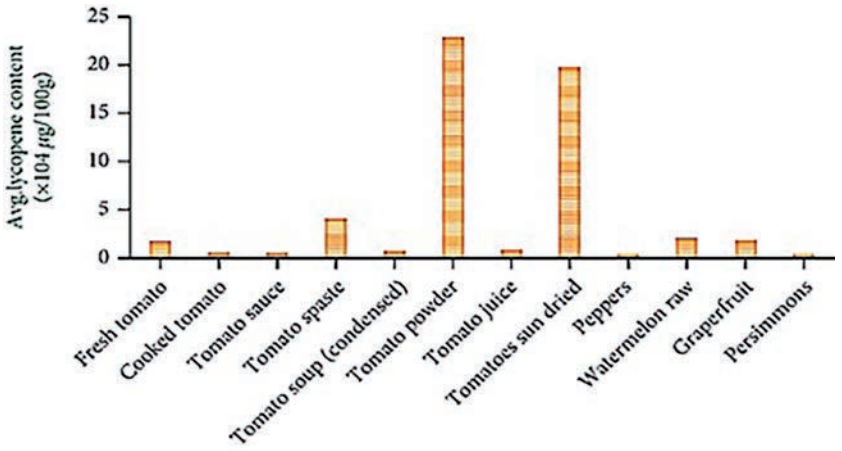

Figure 2.
Average lycopene content in different forms of tomato [9].

The bar graph illustrates the average lycopene content in a variety of food items, expressed as $\times 10^4$ μg per 100 grams. Among the analyzed sources, tomato powder contains the highest concentration of lycopene, followed closely by tomato juice and sun-dried tomatoes. Moderate levels are observed in tomato paste, grapefruit, and fresh tomatoes. Other processed tomato products such as cooked tomato, tomato sauce, and condensed tomato soup exhibit comparatively lower lycopene levels. In contrast, non-tomato foods, including peppers, raw watermelon, and persimmons contain minimal amounts. The x-axis of the graph categorizes the food items, while the y-axis quantifies their respective lycopene concentrations.

Beyond tomatoes, several other food sources provide substantial amounts of lycopene. **Figure 3** presents the top 10 lycopene-rich foods, highlighting the diversity of natural sources available for dietary intake.

"United States Department of Agriculture, Agricultural Research Service. FoodData Central. Beltsville (MD)".

Lycopene absorption follows mechanisms like other lipid-soluble compounds. Ingested lycopene incorporates into dietary lipid micelles and undergoes passive diffusion across the gastrointestinal tract into intestinal mucosal cells. Subsequently, it is incorporated into chylomicrons and transported via the lymphatic system to the liver [10]. "Lycopene is transported via lipoproteins for distribution to various organs. Due to its lipophilic properties, LDL serves as the primary carrier rather than HDL. Typically, 10–30% of dietary lycopene undergoes absorption, with the remainder being excreted. Lycopene bioavailability is enhanced in tomato paste compared to fresh tomatoes, which is attributed to the increased cis-isomeric forms present in processed products" [11].

Individual variations in lycopene absorption and metabolism significantly influence therapeutic outcomes and bioavailability. Genetic polymorphisms in genes encoding carotenoid-cleaving enzymes, lipid transport proteins, and cellular uptake mechanisms contribute to inter-individual differences in lycopene status. These genetic factors may partially explain the variable responses observed in clinical studies and highlight the potential for personalized nutrition approaches.

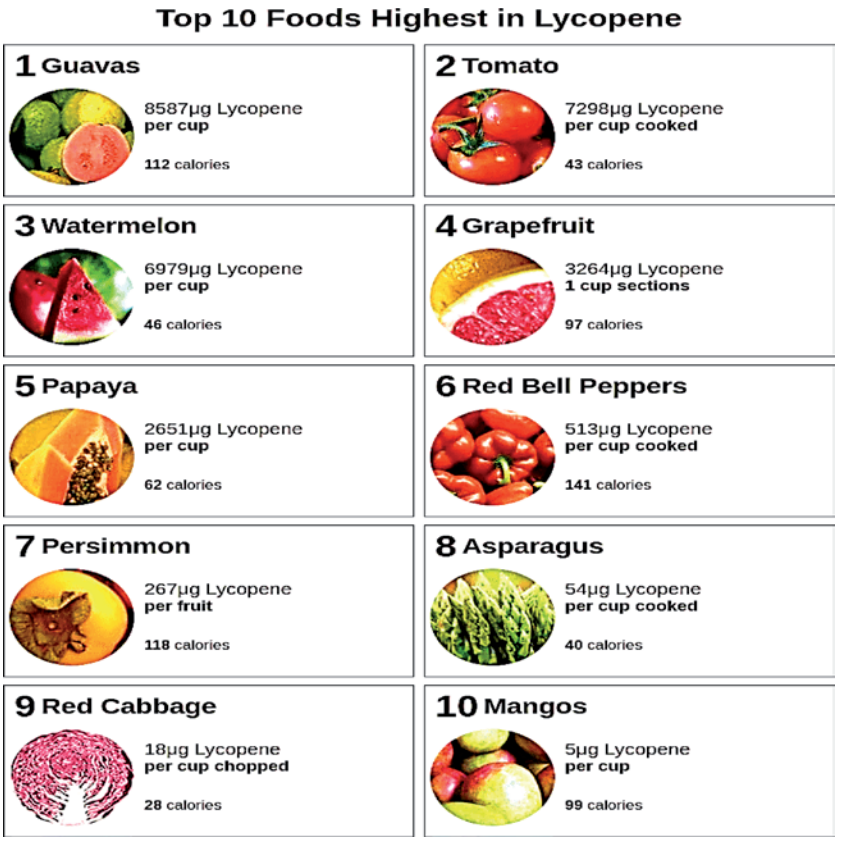

Figure 3.
Top 10 foods rich in lycopene [9].

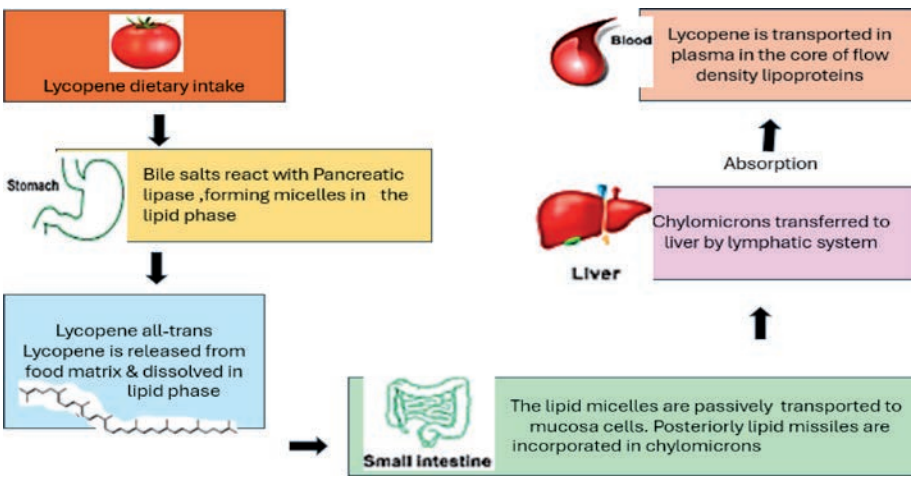

Figure 4.
Lycopene kinetics following oral administration: absorption, distribution, metabolism, and excretion.

Age-related changes in digestive function, including reduced gastric acid production and altered bile acid synthesis, can impair lycopene absorption in elderly populations. Additionally, certain medical conditions affecting lipid absorption, such as inflammatory bowel disease or pancreatic insufficiency, may compromise lycopene bioavailability and require specialized delivery methods or higher doses for therapeutic efficacy.

Lycopene exhibits a complex pharmacokinetic profile from ingestion to cellular utilization. **Figure 4** depicts the complete pathway of lycopene through absorption, distribution, metabolism, and excretion in the human body.

4. Mechanism of action of lycopene

Lycopene, a phytochemical agent, has attracted considerable attention due to its potential to act through a variety of mechanisms of action, such as anti-cancerous, anti-diabetic cardioprotective, anti-hyperlipidemic, anti-inflammatory, hepatoprotective, and antioxidants.

The quantum yield for singlet oxygen quenching by lycopene approaches unity under physiological conditions, making it one of the most efficient biological antioxidants. This exceptional efficiency stems from the compound's ability to physically quench singlet oxygen through energy transfer rather than chemical reaction, allowing the lycopene molecule to be regenerated and reused multiple times. The energy absorbed during quenching is dissipated as heat and triplet-triplet annihilation, preventing damage to surrounding cellular components.

Beyond singlet oxygen, lycopene exhibits significant reactivity toward other reactive oxygen species, including hydroxyl radicals, superoxide anions, and peroxyl radicals. The rate constant for these reactions varies considerably, with hydroxyl radical scavenging occurring at near-diffusion-limited rates. This broad-spectrum antioxidant activity provides comprehensive protection against various forms of oxidative stress encountered in pathological conditions.

It acts by inhibiting glucose and lipid peroxidation and improves systemic antioxidative and inflammatory events. It can prevent cellular damage (hypoxia, physical and chemical agents, aging, and apoptosis) by quenching free oxygen.

The pathophysiology of PCOS involves multiple cellular damage mechanisms primarily driven by oxidative stress. **Figure 5** depicts the cascade of cellular damage associated with PCOS, showing how reactive oxygen species contribute to reproductive dysfunction.

ROS plays a crucial role in modulating reproductive physiological functions, including folliculogenesis, oocyte maturation, ovulation, fertilization, implantation, ovarian steroidogenesis, progesterone production, and luteolytic.

PCOS mitochondrial issues are a key target for lycopene treatment. Ongoing oxidative stress harms mitochondrial DNA, disrupts energy production, and increases ROS. Lycopene's ability to incorporate into mitochondrial membranes and protect against lipid peroxidation helps maintain mitochondrial integrity and function. This mitochondrial protection is particularly important in metabolically active tissues, such as ovaries, where energy demands are high during follicular development and steroidogenesis.

Epigenetic modifications induced by oxidative stress contribute to the perpetuation of PCOS pathophysiology across generations. Lycopene's influence on DNA methylation patterns and histone modifications may help restore normal gene

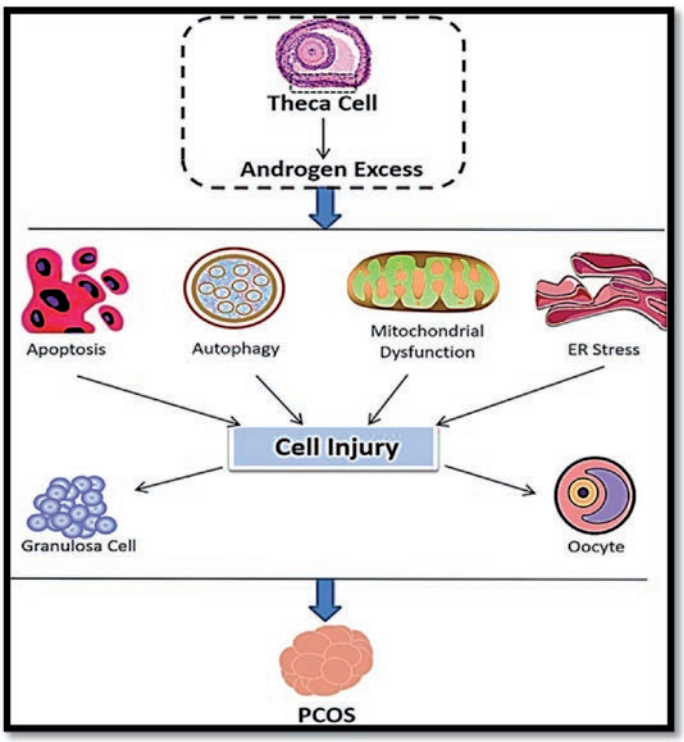

Figure 5.
Cellular damage associated with PCOS [12].

expression patterns and break the cycle of transgenerational PCOS transmission. These epigenetic effects provide additional therapeutic mechanisms beyond direct antioxidant activity.

4.1 Antioxidant properties

"Lycopene's antioxidant effects come from neutralizing reactive oxygen species (ROS). Lycopene supplements or lycopene-rich foods are popular for their health benefits, which protect against metabolic issues such as cardiovascular diseases and type 2 diabetes" [13]. There is also growing evidence about the lycopene ability to mitigate events related to advanced glycation. For all these reasons, lycopene has emerged as an interesting natural bioactive compound. "Lycopene neutralizes free radicals such as hydrogen peroxide, nitrogen dioxide, and hydroxyl radicals. Its antioxidant power is boosted when combined with other tomato compounds, such as β-carotene, phytoene, and phytofluene" [14].

"Lycopene, with its many double bonds, has the strongest ability among carotenoids to neutralize singlet oxygen-free radicals by donating electrons, making it highly reactive" [15]. Lycopene neutralizes singlet oxygen and peroxyl radicals. Its action against reactive oxygen species (ROS) involves three main mechanisms:

i. "Lycopene neutralizes radicals through (1) forming adducts by radical addition, (2) transferring electrons to the radical, and (3) abstracting allylic hydrogen" [11].

ii. "Lycopene boosts the cell's antioxidant system by regenerating non-enzymatic antioxidants, such as vitamins E and C, from their radicals, and it may specifically protect vitamin E" [16].

iii. "Lycopene blocks the insulin-like growth factor 1 receptor (IGF-1R) signaling pathway and the related Ras signaling cascade" [16].

The synergistic interactions between lycopene and other antioxidants create amplified protective effects that exceed the sum of individual components. Vitamin E regeneration by lycopene involves electron transfer from the carotenoid to the tocopherol radical, restoring vitamin E's antioxidant capacity. Similarly, lycopene can interact with vitamin C and glutathione to create antioxidant networks that provide comprehensive cellular protection.

The tissue-specific distribution of lycopene correlates with its protective effects in different organs. The compound shows preferential accumulation in tissues with high-oxidative stress exposure, including prostate, liver, adrenals, and ovaries. This targeted distribution may explain lycopene's particular efficacy in conditions affecting these tissues and suggests optimization strategies for therapeutic applications.

Environmental factors influencing antioxidant status, including air pollution, tobacco smoke, and dietary pro-oxidants, can overwhelm endogenous protective systems and create therapeutic opportunities for lycopene supplementation. The compound's ability to maintain antioxidant capacity under high-oxidative stress conditions makes it particularly valuable for individuals exposed to environmental toxins or suffering from conditions characterized by oxidative imbalance.

Numerous studies have proved lycopene to be fruitful for treating different diseases. The following is a contest of few studies in this regard.

4.2 Anticancer therapeutic mechanisms

"Lycopene also inhibits tumor necrosis factor (TNF)-α release and stimulates interleukin (IL)-10 production [17]. It helps prevent cancers such as prostate, bladder [5], ovarian, cervical, leukemia, oral, esophageal, pancreatic [18], rectal, colon [6], (or digestive tract), lung, bone, and breast. Lycopene also retards the growth of tumors and inhibits tumorigenesis [19]."

The anticancer mechanisms of lycopene extend beyond antioxidant activity to include modulation of cell cycle progression and apoptotic pathways. The compound boosts tumor suppressor genes such as p53 and retinoblastoma protein, while reducing oncogenes such as c-Myc and cyclin D1.These effects result in cell cycle arrest and enhanced apoptosis in malignant cells while sparing normal tissues.

Epidemiological studies have consistently demonstrated inverse correlations between dietary lycopene intake and cancer risk across multiple cancer types. A meta-analysis of prospective cohort studies involving over 250,000 participants showed 10–20% risk reduction for various cancers with high lycopene consumption. The protective effects appear most pronounced for hormone-dependent cancers, suggesting particular relevance for women with PCOS who face increased cancer risks due to hormonal imbalances.

4.3 Anti-inflammatory action

"Lycopene has positive effects on inflammation and redox imbalance due to the activating expression of antioxidant genes and regulating signaling pathways as

inflammatory mediators. It is useful in chronic inflammatory diseases of the lung [14], brain [13], liver [20], and kidney [21]. Lycopene's anti-inflammatory effects include: a) adjusting cyclooxygenase and lipoxygenase levels; b) controlling inducible nitric oxide synthase; and c) blocking NFkB and activator protein-1 [22]." Several research articles are present in this regard [11].

The resolution of inflammation represents an active process requiring specialized mediators, and lycopene appears to promote this resolution phase through multiple mechanisms. The compound enhances the production of specialized pro-resolving mediators (SPMs) derived from omega-3 fatty acids, which facilitate the clearance of inflammatory cells and restoration of tissue homeostasis. This pro-resolution activity distinguishes lycopene from simple anti-inflammatory agents and may contribute to its therapeutic efficacy in chronic inflammatory conditions.

Chronic low-grade inflammation in metabolic syndrome and PCOS involves immune cells, fat tissue, and metabolic organs. Lycopene shifts macrophages from pro-inflammatory M1 to anti-inflammatory M2, restoring immune and metabolic balance through changes in cell metabolism and gene expression.

4.4 Hormonal and metabolic regulation

"It improves insulin resistance and helps in lowering down serum glucose level; here, it also plays an important role as an antioxidant agent [19]. Its hyperlipidemic effect helps make it useful as a cardioprotective drug [18]."

The relationship between lycopene and glucose homeostasis involves multiple cellular targets and signaling pathways. Lycopene enhances insulin receptor sensitivity through the reduction of oxidative-stress-induced receptor modifications and improvement of downstream signaling cascades. The compound also influences glucose transporter expression and translocation, particularly GLUT4 in skeletal muscle and adipose tissue, leading to improved glucose uptake and utilization.

Advanced glycation end products (AGEs), formed in high blood sugar, worsen diabetic complications. Lycopene strongly prevents early glycation and irreversible AGE formation, offering extra protection against diabetic issues beyond just managing blood sugar.

4.5 Skin diseases

"The skin protection mechanisms can be increased by lycopene due to the synthesis of prostaglandins and phospholipids" [21]. Thereby, topical application of lycopene may reduce inflammatory infiltrate. Lycopene (0.05%) applied to the skin significantly reduces swelling and redness. "Lycopene shields skin from UV damage by reducing inflammation, supporting normal cell growth, and preventing DNA harm" [23].

The photoprotective mechanisms of lycopene involve both direct UV absorption and enhancement of endogenous protective systems. The compound's chromophore structure allows absorption of UV radiation in the 280–400 nm range, providing physical protection against photodamage. Additionally, lycopene upregulates the expression of antioxidant enzymes and heat shock proteins in skin cells, enhancing cellular resistance to UV-induced stress.

Skin aging involves complex interactions between intrinsic aging processes and extrinsic factors, such as UV radiation and environmental pollutants. Lycopene's ability to protect collagen and elastin fibers from degradation helps maintain skin structure and elasticity. The compound also stimulates fibroblast proliferation and collagen synthesis, promoting skin repair and regeneration processes.

5. Experimental evidence of lycopene in PCOS model

Recent clinical studies have begun to explore the specific role of lycopene in PCOS management. The oxidative stress associated with PCOS creates an ideal therapeutic target for lycopene intervention. Women with PCOS typically exhibit elevated markers of oxidative stress, including increased malondialdehyde levels and reduced antioxidant enzyme activity. Lycopene supplementation has shown promise in addressing these imbalances by enhancing the body's natural antioxidant defense systems.

In experimental PCOS models, lycopene administration has demonstrated significant improvements in ovarian morphology, with reduced cystic follicles and restored normal follicular development. The compound's anti-inflammatory properties help reduce the chronic low-grade inflammation characteristic of PCOS, potentially improving insulin sensitivity and hormonal balance. Furthermore, lycopene's ability to modulate steroidogenesis may contribute to the normalization of androgen levels in PCOS patients.

The optimal dosage of lycopene for therapeutic purposes varies depending on the condition being treated and the form of administration. For general health maintenance, dietary intake of 5–10 mg per day through food sources is typically recommended. However, for therapeutic applications in conditions like PCOS, higher doses ranging from 15 to 30 mg per day may be beneficial. Lycopene is generally well-tolerated with minimal side effects reported in clinical studies.

Safety profiles indicate that lycopene supplementation is safe for most individuals, with no significant adverse effects reported at recommended doses. However, individuals taking certain medications or those with specific medical conditions should consult healthcare providers before initiating lycopene supplementation. The lipophilic nature of lycopene means that absorption is enhanced when consumed with dietary fats, making timing of administration an important consideration for optimal bioavailability.

Incorporating lycopene into PCOS management strategies requires a comprehensive approach that considers both dietary and supplemental sources. Healthcare providers should assess patients' current dietary intake of lycopene-rich foods and provide guidance on optimizing consumption. Patient education regarding food preparation methods that enhance lycopene bioavailability, such as cooking tomatoes and consuming them with healthy fats, is essential for maximizing therapeutic benefits.

Monitoring protocols should be established to track patient's response to lycopene intervention, including assessment of oxidative stress markers, hormonal profiles, and clinical symptoms. Regular follow-up appointments allow for dosage adjustments and evaluation of treatment efficacy. The integration of lycopene therapy with existing PCOS management approaches, including lifestyle modifications and conventional medications, requires careful coordination to ensure optimal patient outcomes.

6. Comparison with other antioxidants in PCOS

Lycopene's role compares favorably to other antioxidants:

- Vitamin E: Mitigates oxidative stress but has limited impact on insulin sensitivity; combining it with lycopene may enhance effects.
- N-acetylcysteine (NAC): Boosts insulin sensitivity and ovulation but lacks lycopene's anti-inflammatory strength.
- Coenzyme Q10: Supports mitochondrial function and lipid profiles but offers less hormonal regulation.
- Myo-inositol: Excels in improving insulin signaling and ovulation but is less effective against inflammation.

7. Conclusion

Lycopene stands out as a powerful, naturally occurring antioxidant with wide-ranging therapeutic potential, particularly in the management of PCOS. Lycopene effectively neutralizes reactive oxygen species (ROS) by acting as a potent antioxidant, scavenging free radicals such as singlet oxygen and peroxyl radicals, modulating inflammatory pathways, and supporting endocrine balance, which makes it a promising candidate for adjunct therapy. Experimental models have demonstrated its positive effects on histological, hormonal, and metabolic parameters associated with PCOS. Unlike many pharmaceutical agents, lycopene is widely available through common dietary sources and is both safe and cost-effective. Given its broad-spectrum action and accessibility, lycopene offers a compelling natural option in addressing the complex pathophysiology of PCOS and warrants further exploration in clinical settings.

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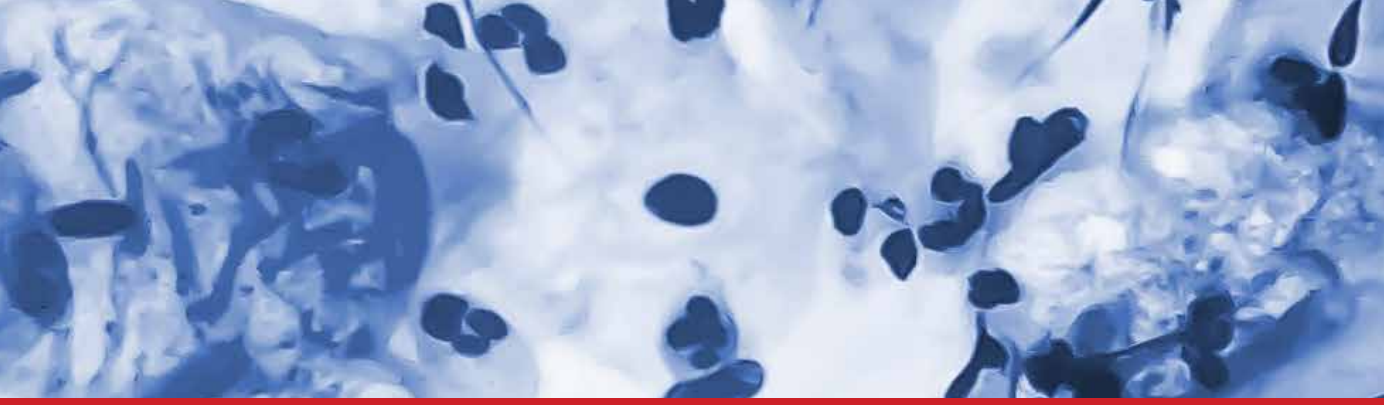

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Polycystic Ovary Syndrome (PCOS) is one of the most common yet complex endocrine disorders affecting women of reproductive age, impacting not only fertility, but also metabolism, hormonal balance, and long-term health. *Understanding Polycystic Ovary Syndrome – Symptoms, Diagnosis, and Treatment Options* offers a clear, evidence-based, and multidimensional exploration of this condition. This comprehensive volume brings together the latest scientific discoveries and clinical insights to help readers understand the biological, diagnostic, and therapeutic aspects of PCOS. Section 1 introduces PCOS from a holistic perspective, outlining its pathophysiology and systemic impact. Section 2 delves into the diverse manifestations of PCOS, from ovulatory dysfunction and menstrual irregularities to metabolic disturbances, insulin resistance, and urological complications that are often overlooked in clinical practice. Section 3 explores state-of-the-art diagnostic approaches, including advances in artificial intelligence, genetic risk profiling, imaging technologies, and biochemical evaluation. Section 4 highlights both conventional and emerging treatment strategies, spanning lifestyle interventions, pharmacologic therapies, bariatric surgery, and novel agents such as myoinositol and lycopene. Whether you are a clinician, researcher, medical student, or a woman seeking to better understand her health, this book provides the essential knowledge needed to navigate PCOS with confidence. It bridges the gap between scientific research and patient-centered care, empowering readers to recognize, diagnose, and manage PCOS more effectively in the modern era of personalized medicine.

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