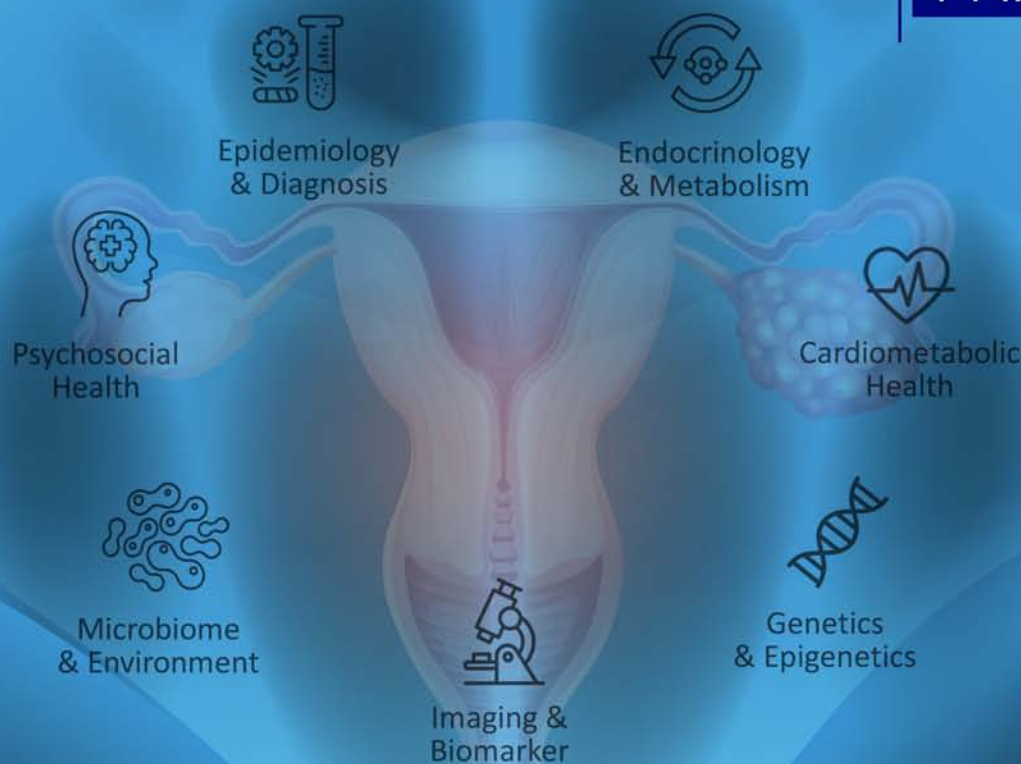


# CURRENT AND EMERGING CONCEPTS OF POLYCYSTIC OVARY SYNDROME MANUAL FROM M.P. PCOS SOCIETY

PART 1



Editors:

**Mohammad Ashraf Ganie**

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**Rakesh Kumar Sahay**

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**Imtiyaz Ahmad Wani**



M.P.PCOS

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**Current and Emerging Concepts of Polycystic  
Ovary Syndrome–Manual from M.P.  
PCOS Society**

*(Part 1)*

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## FOREWORD I

The inaugural edition of "Current and Emerging Concepts of Polycystic Ovary Syndrome-Manual from the M.P. PCOS Society", stands as a testament to the unwavering commitment of the Chief Editor and his team to advancing medical science, particularly in the field of women's reproductive health. Their dedication aligns closely with the Prime Minister Narendra Modi led Government of India's priority on women-centric healthcare and the nation's growing focus on the prevention and management of non-communicable diseases.

This comprehensive book is therefore both timely and essential, arriving at a critical juncture when endocrine and metabolic disorders, particularly Polycystic Ovary Syndrome (PCOS), are emerging as pressing public health concerns in India.

With India undergoing an epidemiological transition, we need to respond to health challenges with a proactive, multidisciplinary approach. PCOS, being a complex condition with metabolic, reproductive, endocrine, and psychosocial implications, exemplifies the kind of health challenge that warrants an integrated perspective. This manual, developed through the M.P. PCOS Society and drawn from the foundational work of the Indian Council of Medical Research (ICMR) National Task Force Study on PCOS, is a fine reflection of that perspective.

Particularly notable is the emphasis of this manual on the integration of Artificial Intelligence, lifestyle medicine, and public health policy into clinical care, areas that resonate closely with the Government of India's vision for a digitally empowered, health-secure nation. Besides, the content of the manual is interesting for the readers, including clinicians, postgraduate students, researchers, and allied health professionals, for addressing this complex syndrome.

I hope this manual stands as a knowledge repository and reaffirms our national commitment to prioritizing women's health, combating non-communicable diseases, and promoting research that is attuned to the needs of our population.

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## FOREWORD II

It is with a deep sense of purpose and professional pride that I pen this foreword for the first edition of the manual titled “*Current and Emerging Concepts of Polycystic Ovary Syndrome – Manual from M.P. PCOS Society*”, published by Bentham Science Publishers. This comprehensive publication marks a significant milestone in the ongoing endeavor to address Polycystic Ovary Syndrome (PCOS), one of the most prevalent and complex endocrine-metabolic disorders affecting women of reproductive age.

The Indian Council of Medical Research (ICMR)-Task Force initiative on PCOS played a catalytic role in uncovering the magnitude of this condition and generating a wealth of data that may pave the way in framing the national research agenda around it. This Manual from the M.P. PCOS Society has seamlessly integrated the biological, clinical, and psychosocial dimensions of PCOS. With contributions from distinguished experts, meticulously structured chapters serve not only as an academic repository but also as a strategic guide for clinicians and researchers. It underscores the need for a holistic, ethnically contextualized, and evidence-based approach in the diagnosis, management, and research of PCOS.

In an era marked by an alarming rise in lifestyle-related disorders, the insights provided in this manual are especially pertinent. From elucidating the pathophysiological underpinnings of PCOS to exploring emerging therapeutic modalities, including the use of artificial intelligence in diagnosis and care, the breadth and depth of this book are commendable. Its publication is timely and imperative, particularly as we work to align women's health initiatives with broader goals of preventive medicine and metabolic health.

I congratulate the chief editor, editors, and the entire M.P. PCOS Society for their vision and scholarly commitment. This manual is a testament to what collaborative scientific endeavors can achieve and will serve as an indispensable resource, boosting further research in the field of PCOS.

**Vinod Paul**  
Government of India  
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New Delhi, India

## PREFACE

We warmly welcome revered readers to the inaugural edition of "*Current and Emerging Concepts of Polycystic Ovary Syndrome (PCOS) – Manual from M.P. PCOS Society.*" We are thrilled to present this meticulously crafted compendium amidst a rising global tide of PCOS, now recognized as a complex endocrine-metabolic disorder with far-reaching reproductive and psychological implications. The **M.P. PCOS Society India** has remained steadfast in its mission to foster collaborative research, facilitate interdisciplinary knowledge exchange, and elevate public consciousness. This manual stands as a reflection of that commitment, an academic and clinical resource curated to support healthcare professionals, researchers, and affected individuals alike in navigating the intricacies of PCOS. Given the depth and diversity of the content, this manual has been thoughtfully divided into two parts, each complementing the other, to provide a more comprehensive and accessible reference on both the foundational understanding and evolving paradigms in PCOS. Part I of this book offers a comprehensive exploration of the epidemiological patterns, diagnostic complexities, and intricate pathophysiological foundations of PCOS. From its historical evolution to contemporary insights into genetic, epigenetic, metabolic, endocrine, and microbial influences, this book brings together the collective expertise of distinguished clinicians, researchers, and educators from across India and South Asia. What distinguishes this manual is not only its scientific rigor but also its interdisciplinary breadth, drawing perspectives from endocrinology, dermatology, psychiatry, reproductive biology, radiology, and public health. Particular focus is placed on diagnostic challenges in special populations, the diversity of cutaneous presentations, and the syndrome's clinical variability across ethnic and geographic contexts. We extend our sincere gratitude to all contributors whose intellectual dedication and academic excellence have made this book a valuable resource for clinicians, postgraduate students, researchers, and public health professionals. We hope part I will serve not only as a repository of knowledge but also as a source of inspiration, encouraging continued research, promoting earlier and more accurate diagnosis, and fostering informed conversations that place women's metabolic, reproductive, and psychological health at the forefront of care.

**With deep gratitude and scientific resolve.**

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**CHAPTER 1**

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**Introduction and Historical Aspects of PCOS****Ashutosh Halder<sup>1,\*</sup>**<sup>1</sup> *Department of Reproductive Biology, AIIMS, New Delhi, India*

**Abstract:** The most prevalent reproductive endocrine condition affecting women of reproductive age is called polycystic ovary syndrome, or PCOS. Hyperandrogenism, irregular ovulation, and polycystic ovarian shape are the hallmarks of PCOS. Despite the fact that PCOS has been recognized for more than a century, there is ongoing debate over its diagnosis, origin, clinical characteristics, and course of therapy. The first scientific study of (PCOS) was conducted in 1935 by Stein and Leventhal, although Vallisneri provided the first account of PCOS in 1721, marking the historical evolution of the syndrome. The first scientific PCOS diagnostic criteria were proposed in 1990 at an NIH-sponsored conference. The syndrome is most often known as Polycystic Ovary Syndrome (PCOS), and the NIH 2012 criteria are now the mainstream diagnostic standards used, *i.e.*, Rotterdam 2003 criteria with phenotypic classification. The last guideline on PCOS, *i.e.*, the international evidence-based policy (2018), amended in 2023, is acceptable to all groups working on PCOS. AMH may be the most effective biomarker currently identified for PCOS. Complex and heterogeneous, PCOS is influenced by environmental and epigenetic factors in addition to genetic vulnerability. This chapter on PCOS aims to provide an introductory note along with the historical evolution of PCOS.

**Keywords:** Abnormal ovulation, Consensus diagnostic standards, Hyperandrogenism, Polycystic ovarian anatomy, Polycystic ovary syndrome.

**INTRODUCTION**

A complex reproductive condition known as Polycystic Ovarian Syndrome (PCOS) is typified by polycystic ovary morphology (polycystic and/or enlarged ovary), chronic oligo-ovulation or anovulation (oligomenorrhoea or amenorrhoea), and hyperandrogenism (hirsutism and/or elevated androgens). For women who are of reproductive age, it is the most prevalent reproductive endocrine condition. According to reports, its prevalence ranges from 8–15% in women who are of reproductive age and is roughly 21% in women who are at high risk (*e.g.*, infer-

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tile) [1 - 3]. The Rotterdam 2003 criteria with phenotypic classification, or the NIH 2012 criteria, are the most widely accepted diagnostic standards [4, 5]. One of the key characteristics of the syndrome is hyperandrogenism; however, none of the PCOS recommendations, especially the cut-off values for biochemical hyperandrogenism, are clearly stated. The optimal androgen, the estimation technique, and the cut-off value remain unsettled. The most effective biomarker for PCOS that is currently available is the AMH, which was included in updated diagnostic criteria 2023 [6]. PCOS is significantly correlated with endogenous variables like melatonin and kisspeptin, as well as environmental pollutants like AGEs and bisphenol A [7]. Overweight individuals with PCOS are approximately 50% more likely to experience infertility, insulin resistance, decreased glucose tolerance, and endometrial hyperplasia [8]. It appears that there is a wide range of underlying causes for PCOS in humans, and environmental and genetic factors are likely to play a role in epigenetics (the regulation of gene expression) [7, 9]. Despite certain correlation studies, the exact genetic etiology of PCOS is still unknown [10]. Environmental contaminants may also have an impact since endocrine-disrupting substances can alter ovarian and metabolic function, leading to abnormalities similar to PCOS [7]. An outline of the historical elements of the syndrome's (PCOS) evolution, including nomenclature and diagnostic criteria, will be given in this chapter.

### **Historical Aspects**

The earliest account of PCOS dates back to 1721 and comes from a case report by Vallisneri [11]. Italian physician, scientist, and naturalist Vallisneri reported on a married infertile woman who was obese and had a big, shining, white ovary that was likened to an egg from a pigeon [11]. Chereau provided the second description of the condition in 1844 [12]. Chereau, a French physician, described ovaries with the disorder as fibrous and sclerotic with hydropic follicles (sclerocystic ovary) [12]. This ovarian description was very similar to Rokitansky's [13]. Rokitansky reported hydrops follicles and fibrous and sclerotic lesions in ovaries with a degenerative nature [13]. Subsequently, ovarian pathology was characterized by a number of authors as microcystic ovaries, hyperthecosis of the ovary, and other conditions [14]. Since, the ovaries were the main focus of all of these earlier reports, ovarian pathology—either swollen, polycystic, or sclerotic—was implied to be linked to the illness. Subsequently, the condition was briefly associated with elevated levels of testosterone and LH as crucial diagnostic indicators, but this association was eventually dropped [15, 16]. A summary of the significant moments in PCOS history can be seen in Table 1.

Table 1. Polycystic ovary syndrome historical markers.

Landmarks	Author	Year
Overview and background information about PCOS Markers The disorder's first clinical description was found in a case report involving an obese woman who was infertile and had a big, shining, white ovary resembling a pigeon egg	Vallisneri A [11]	1721
Sclerotic, fibrous ovary with hydropic follicles (sclerocystic ovary)	Chereau A [12]	1844
Cystic degeneration of the ovary	Rokitansky [13]	1855
Hyperthecosis of ovary	Bulius and Kretschmar	1897
Microcystic ovaries	McGlenn JA [14]	1916
Stein-Leventhal syndrome, which is linked to amenorrhea and bilateral polycystic ovaries (the first scientific description of PCOS)	Stein and Leventhal [17]	1935
Menstrual irregularities, polycystic ovaries, and hirsutism: hyperthecosis (the significance of clinical hyperandrogenism)	du Toit DAH [18]	1951
Sclerotic polycystic ovary	Davis CD, <i>et al.</i> [19]	1956
Polycystic ovary syndrome	Keettel WC [20]	1957
Polycystic ovarian disease	Evans and Riley [21]	1958
Polycystic ovary disease	Lambeth and Kintner [22]	1959
Polycystic ovarian syndrome	Cook WS [23]	1965
Linked with inappropriate secretion of gonadotropins	Yen SSC, <i>et al.</i> [15]	1970
Ovarian Micro-polycystic syndrome	Vokaer R [24]	1977

In 1935, Stein and Leventhal published the first scientific description of PCOS under the moniker “amenorrhea associated with bilateral polycystic ovaries” (17). The authors (Stein and Leventhal, USA) described seven cases of infertility in females with bilateral enlarged polycystic ovary and menstrual disturbance (oligomenorrhoea in two patients and amenorrhoea in five patients). Urine 17-ketosteroids (to rule out gonadotropin, premature ovarian failure/menopause, congenital adrenal hyperplasia, androgen-producing tumors, or hyperandrogenaemia of any etiology), as well as congenital adrenal hyperplasia, were normal. The writers also discussed clinical observations such as tiny breasts, small uterus, and hirsutism. About 50% of the women had hirsutism, and about 75% had smaller-than-normal breast and/or uterine sizes. This indicates that 75% of the women had clinical hyperandrogenism, and 25% did not [17].

About 50% of the women had hirsutism, and about 75% had smaller-than-normal breast and/or uterine sizes. This indicates that 75% of the women had clinical hyperandrogenism, and 25% did not, according to Stein and Leventhal (USA). However, their paper's lack of emphasis on clinical or biochemical

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**CHAPTER 2**

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**Epidemiology of PCOS****Mohammad Ashraf Ganie<sup>1,\*</sup>, Imtiyaz Ahmad Wani<sup>1</sup> and Tasleem Arif<sup>1</sup>**<sup>1</sup> *Department of Endocrinology and Clinical Research, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, J&K, India*

**Abstract:** Polycystic Ovary Syndrome (PCOS) affects women of reproductive age worldwide, showing varied prevalence rates depending on the diagnostic criteria utilized. It is also thought to be influenced by race and ethnicity. Ethnic and geographical variations in its prevalence and presentation highlight the multifactorial nature of the syndrome. The economic burden of PCOS extends beyond healthcare costs to encompass its impact on Quality of Life (QoL) and is associated with significantly higher risks of obesity, dyslipidemia, Impaired Glucose Tolerance (IGT), and long-term complications such as diabetes, cardiovascular disease, *etc.* Recognizing PCOS as a global health priority necessitates multifaceted approaches to improve awareness, diagnosis, and management worldwide. This chapter presents the current knowledge on the epidemiological aspects of PCOS and its prevalence based on the different diagnostic criteria—American Society for Reproductive Medicine (ASRM) (Rotterdam 2003), National Institutes of Health (NIH) 1990, European Society of Human Reproduction (ESHRE), and Androgen Excess and PCOS (AE-PCOS) Society 2006 – estimated in different populations. The evidence-based data regarding the relationship between PCOS provides valuable insights, and race and ethnicity are also discussed. Finally, this chapter provides an overview of the economic burden of PCOS as well as ethnic and geographic variations in the prevalence of PCOS, drawing insights from key research findings.

**Keywords:** Diagnostic criteria, Epidemiology, Ethnicity, Economic burden, Prevalence.

**INTRODUCTION**

Polycystic Ovary Syndrome (PCOS), still a “syndrome”, is a collection of signs and features that characterize a disorder, where no single test is diagnostic. The principal features of PCOS include androgen excess, ovulatory dysfunction, and/or polycystic ovaries. It is now emerging as a major health concern among reproductive-age women globally [1, 2].

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PCOS is relatively heterogeneous and these principal features have been combined in various manners to arrive at specific criteria for PCOS for its diagnosis. Given the heterogeneity in presentation and diagnostic criteria, the quantitation of its burden is a global challenge. Diagnosis of PCOS should not be taken lightly, for this syndrome is associated with significant fear of other health issues. PCOS has emerged now as an endocrine–metabolic disorder associated with a barrage of metabolic dysfunctions such as Abnormal Glucose Tolerance (AGT), obesity, Metabolic Syndrome (MS), increased risk of Cardiovascular Disease (CVD), Non-Alcoholic Fatty Liver Disease (NAFLD), mitotic risk, cosmetic problems, *etc.*, and thus the condition is currently of prime focus in research [3 - 5]. Oligo-Anovulation (OA), clinical and/or biochemical hyperandrogenism (HA), and Polycystic Ovarian Morphology (PCOM) as its defining features, PCOS appears to be a significant contributor to many Non-Communicable Diseases (NCDs), including Type 2 Diabetes Mellitus (T2DM), NAFLD, cancers, and psychological disorders. The high prevalence of PCOS and its association with ovulation, menstrual disorders, infertility, and a barrage of metabolic complications make it a significant public health concern and highlight the large financial burden caused by PCOS [6, 7]. Understanding the epidemiologic profile of PCOS, ethnic and geographic variations, and its economic burden is essential for healthcare providers to recognize the condition promptly, implement appropriate diagnostic and management strategies, and address the multifaceted needs of individuals affected by PCOS.

### **PCOS Historical Overview**

The term PCOS came into existence some 88 years ago and was named so based on ovarian morphology. In 1935, Stein and Leventhal first described seven women suffering from amenorrhea, hirsutism, and enlarged ovaries with multiple cysts [8]. Despite extensive research in this field, PCOS is considered a misnomer, and researchers have expressed the need to change the name; a suitable new name has not yet been established. The evolution of PCOS is summarized in Fig. (1).

With advancements in research, cutting-edge technology like ultrasonography to scan ovaries was a game changer in the history of PCOS, simplifying the diagnosis. However, this resulted in an unanticipated outcome: many women were diagnosed with minimal or no additional PCOS symptoms but polycystic ovaries. This gave rise to the term Polycystic Ovarian Morphology (PCOM), whose importance is still debated. It has been argued that widespread acceptance of the Rotterdam criteria, which include oligo-anovulatory women with PCOM who do not have clinical or biochemical evidence of hyperandrogenism, is premature and will result in unnecessary diagnosis and laboratory evaluation and potentially

lifelong consequences for these women. Even after so many years of knowledge, the exact etiology of this ailment is unknown, although it is assumed to be complicated, with a strong genetic component. Although Insulin Resistance (IR) is observed in women with PCOS, it is not one of the diagnostic criteria.

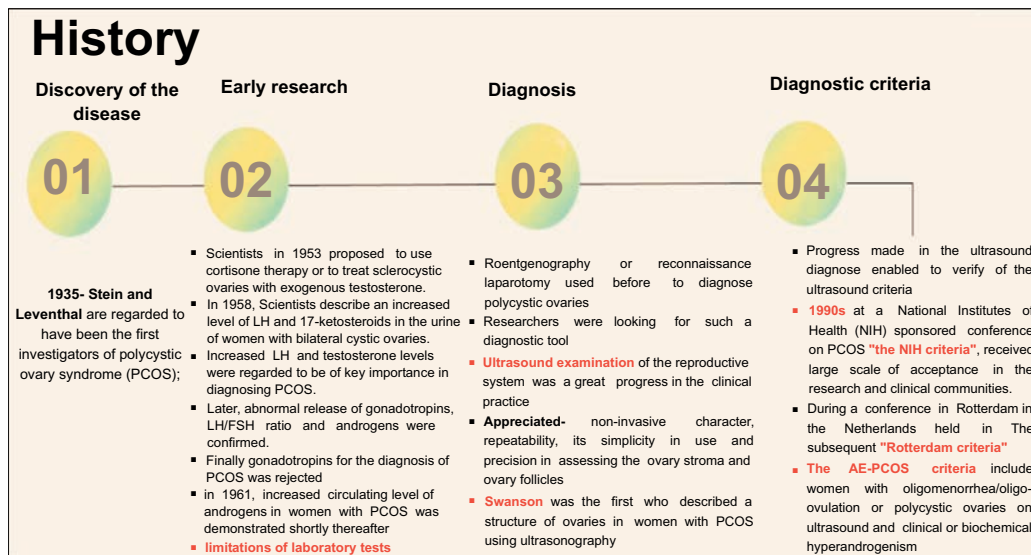


Fig. (1). Schematic depiction of the evolution of PCOS.

## Epidemiology Profile of PCOS

PCOS is the most common endocrine pathology in reproductive-aged females worldwide. It commonly manifests during adolescence or early adulthood, but symptoms can persist throughout a woman's reproductive years and beyond. It shows significant variance in its prevalence depending on the population studied and diagnostic criteria. Rotterdam criteria include a broader prevalence than the NIH Criteria. Based on the NIH criteria and Rotterdam 2003 criteria, the global prevalence rate of PCOS is in the range of 4-21%, in which 5.6% of the PCOS cases account for Chinese women aged 19-45 years [9, 10]. PCOS is prevalent, with an average prevalence of 276.4 cases per 100,000 people in Europe. Around 50% of women are not aware that they have PCOS or have a delayed diagnosis [11]. A nationwide epidemiological survey on the prevalence of PCOS in reproductive-aged women in China has shown a weighted prevalence of 7.8% among women aged 20-49 years, leading to an estimate of 24.0 million women affected in China [12].

To date, the exact prevalence of PCOS in India is unknown due to a lack of well-defined diagnostic criteria and a paucity of data. However, several undersized,

## Diagnostic Criteria of PCOS: Future Challenges and Controversies

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**Abstract:** Though PCOS is a common endocrine disorder, there are controversies related to diagnosis and management. Hyperandrogenism with anovulation has always been indicative of PCOS. Though these symptoms are common in women with PCOS, neither is regarded as an absolute criterion for the diagnosis. With the introduction of ultrasound criteria, there has been an extension to the spectrum of PCOS. To date, there is no clear-cut definition of clinical and biochemical hyperandrogenemia questioning their role in the diagnosis. Subjective assessment of hirsutism and polycystic ovarian morphology again questions the reliability of these modalities. Diagnosis of PCOS in adolescence and perimenopause is again a challenge. In this review, we detail the controversies related to the diagnosis and elaborate on other novel modalities that can assist in the diagnosis.

**Keywords:** 11 oxygenated androgens, Acne, Adolescence, AMH, Antral follicle count, Assay interference, Biochemical hyperandrogenism, Clinical hyperandrogenism, Endocrine disruptors, Hirsutism, Insulin resistance, Menstruation disturbances, MiRNA, Ovarian volume, Oxidative stress markers, Perimenopause, Polycystic ovary syndrome, Rotterdam criteria, SHBG, Ultrasonography.

### INTRODUCTION

There has been a change in the diagnostic criteria of PCOS over the years. The first diagnostic criteria for PCOS were published by the National Institutes of Health, which was based on consensus expert opinion rather than clinical evidence. They defined PCOS as a combination of oligo-anovulation and

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androgen excess after ruling out other causes of anovulatory infertility [1]. They recommended that ultrasound features for polycystic ovaries should be considered as ‘suggestive’ but not diagnostic.

In 2003, an amendment to NIH criteria was made by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) in which they included ultrasound criteria as the third diagnostic criteria [2]. According to this, an ovary was considered polycystic if the Ovarian Volume (OV) was greater than 10 cm<sup>3</sup> and/or the number of follicles (FNPO) measuring 2–9 mm was  $\geq 12$  per ovary. This was named as Rotterdam Criteria, which has been endorsed by the global PCOS guideline published in 2018. This was based on the evidence that polycystic ovaries were concordant in women with biochemical or clinical evidence of the syndrome. Following the diagnosis as per Rotterdam Criteria, women with PCOS can be subdivided into four phenotypes, A to D, as mentioned in Table 1. “Classic PCOS” includes phenotypes A and B, the phenotype C is called “ovulatory PCOS”, and phenotype D is indicated as “non-hyperandrogenic PCOS” [3]. There has been a proposal that PCOS without hyperandrogenism needs to be excluded from the syndrome as it is based on different etiologies [3]. A clustering study by Dapas *et al.* [4] identified two major subtypes of PCOS: a “reproductive” group with high LH and SHBG but with normal/low BMI and normal insulin levels, and a “metabolic” group characterized by high BMI, glucose, and insulin levels, but with low LH and SHBG levels. This study revealed alleles at four loci associated with the “reproductive” subtype and one locus significantly associated with the “metabolic” subtype. The limitation of the study was the influence of the clinical picture by age, ethnicity, and environmental factors. Clinically, at diagnosis, characterization of the specific phenotype is not considered, though there is a cardiometabolic implication of the same. However, this point is still debatable [5]. It was noted that those with androgenic phenotypes had more severe metabolic dysfunction [1]. Adiposity was a major confounder as more severe complications were associated with increasing adiposity, and not all studies controlled for BMI [1].

**Table 1. Phenotypes of PCOS based on rotterdam criteria.**

Phenotype	Androgen Excess	Ovulatory Dysfunction	PCOM on Ultrasound
A	✓	✓	✓
B	✓	✓	-
C	✓	-	✓
D	-	✓	✓

Androgen Excess Society (AES) in 2006 recommended that the initial criteria suggested by NIH is acceptable with few modifications as recommended in the 2003 Rotterdam Conference [6]. According to this guideline, nine phenotypes were suggested based on anovulation/oligo-ovulation, clinical hirsutism, biochemical hyperandrogenism, and ultrasound features [7], as shown in Table 2.

**Table 2. Possible phenotypes of PCOS.**

-	A	B	C	D	E	F	G	H	I
<b>Hyperandrogenemia</b>	+	+	+	+	-	-	+	-	+
<b>Hirsutism</b>	+	+	-	-	+	+	+	+	-
<b>Oligo-anovulation</b>	+	+	+	+	+	+	-	-	-
<b>Polycystic ovaries</b>	+	-	+	-	+	-	+	+	+
<b>NIH 1990 Criteria</b>	✓	✓	✓	✓	✓	✓	-	-	-
<b>Rotterdam 2003 Criteria</b>	✓	✓	✓	✓	✓	✓	✓	✓	✓
<b>AES 2006 Criteria</b>	✓	✓	✓	✓	✓	✓	✓	✓	✓
<b>Suggested clinical study criteria</b>	✓	✓	✓	✓	✓	✓	-	-	-

**Table 3. Diagnostic criteria for PCOS.**

<p><b>1990 NIH guidelines:</b>            Patient satisfies both criteria:            (1) Clinical or biochemical hyperandrogenism            (2) Oligomenorrhoea or oligo-ovulation            Other causes of hyperandrogenism and anovulatory subfertility should be excluded.</p>
<p><b>2003 ESHRE/ASRM or Rotterdam guidelines:</b>            Patient satisfies two of three criteria:            (1) Oligomenorrhoea or oligo-ovulation            (2) Clinical or biochemical hyperandrogenism            (3) Polycystic ovaries on ultrasound            Other causes of hyperandrogenism and anovulatory subfertility should be excluded.</p>
<p><b>2006 AES guidelines:</b>            Patient satisfies both criteria:            (1) Hyperandrogenism: hirsutism or biochemical hyperandrogenism            (2) Ovarian dysfunction: oligo-anovulation or polycystic ovaries            Other causes of hyperandrogenism and anovulatory subfertility should be excluded.</p>

Though the Rotterdam criteria are the most commonly used and widely accepted, there are several controversies that exist in the diagnosis. Recently, efforts have been made to overcome these controversies from previous criteria mentioned in Table 3. This article summarizes the controversies commonly arising in the diagnosis of PCOS.

## Diagnosis of PCOS in Special Situations

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**Abstract:** The generally accepted Rotterdam criteria for diagnosing PCOS should include two of the following criteria: chronic anovulation, Hyperandrogenism (HA) (clinical/biologic), and polycystic ovaries on ultrasound, leading to four types of clinical presentations. It is a challenge to use the adult reproductive phase criteria for diagnosing PCOS in the non-reproductive phase of life. Recently, there has been a consensus on the diagnostic criteria for PCOS in adolescence. In adolescence, hormonal fluctuations and irregular menstrual cycles can mimic PCOS symptoms, necessitating careful evaluation to distinguish physiological changes from pathological ones. Conversely, menopausal transitions can obscure PCOS diagnosis due to overlapping symptoms such as menstrual irregularities and hormonal imbalances. Pregnancy introduces additional complexities, as hormonal changes and gestational conditions may mimic or obscure PCOS symptoms, requiring nuanced diagnostic approaches. Moreover, PCOS often coexists with other metabolic and reproductive disorders, such as thyroid dysfunction and endometriosis, further complicating diagnosis and management. This chapter describes the differential diagnosis strategies for the accurate identification of PCOS in these intricate scenarios.

**Keywords:** Adolescents, Diagnosis, Menopause, Pregnancy, PCOS.

### INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) in an adult woman essentially is a triad of hyperandrogenism, ovulatory dysfunction, and Polycystic Ovarian Morphology (PCOM). The generally accepted Rotterdam criteria for diagnosing PCOS should include two of the following criteria: chronic anovulation, Hyperandrogenism (HA) (clinical/biologic), and polycystic ovaries on ultrasound, leading to four types of clinical presentations and ruling out other causes affecting ovulation or hyperandrogenism [1, 2]. There is universal agreement that PCOS is a primary functional ovarian hyperandrogenism condition. PCOS is a syndrome and not a

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disease affecting the endocrine, menstrual, reproductive, dermatological, and metabolic health with immediate and long-term implications. A syndrome is a constellation of signs and symptoms that are grouped together. The etiology, course, and management may not be very clear and need to be individualized. A disease is a problem with a known specific etiology, a distinct course, and established treatments.

The normal physiological changes in androgen levels, menstrual cycle patterns, and ovarian morphology over the lifespan make the application of the traditional diagnostic criteria challenging in the physiological non-ovulatory phases of a woman's life. Adolescents have an immature hypothalamic-pituitary axis, leading to menstrual irregularities and polycystic ovarian pictures on ultrasound. The clinical signs of hyperandrogenism, hirsutism, and acne are common in the pubertal period. As such, biochemical hyperandrogenism measured by testosterone concentrations has limitations in adults, and the interpretation may be more challenging in adolescents. During anovulatory cycles, the serum concentrations of testosterone rise, and normograms for serum testosterone levels in adolescent females are not available, making the task of biochemical interpretation of Hypothalamic Amenorrhea (HA) difficult.

### **Diagnostic Criteria in Adolescents**

In adolescents, the criteria for diagnosing polycystic ovary syndrome, as per the International consensus, are persistent ovulatory dysfunction without a precipitating cause, as reflected by menstrual dysfunction that is not normal for age at presentation, symptoms that persist beyond one or two years beyond menarche, and HA based on clinical (moderate or severe hirsutism) and /or biochemical (elevated serum total testosterone or free testosterone by specialty reference assay) diagnosis [3]. Within eight years of menarche, ultrasound should not be used as a diagnostic tool to diagnose PCOS [4].

There is consensus from three groups of international experts on published recommendations for the diagnosis of adolescent PCOS [2, 5, 6]. There is agreement about the persistent ovulatory dysfunction without a cause, as shown by a menstrual dysfunction that is not normal for age at presentation of HA based on clinical and /or biochemical diagnosis. Ultrasound-based polycystic ovarian morphology without androgen excess or menstrual dysfunction should not be used to diagnose adolescent PCOS. There is a consensus that adolescents within one to two years after menarche and with symptoms of PCOS are labeled as “at risk for PCOS”. These adolescents are managed according to their symptoms with a vigilant follow-up. Hyperinsulinemia, insulin resistance, and obesity may be present in adolescents with PCOS but are not considered diagnostic criteria. The

question remains whether obese adolescents with ovarian hyperandrogenism in the absence of overt clinical HA and anovulatory symptoms should be considered a variant. The differences in opinion are whether a menstrual dysfunction should persist for a year or two to be considered PCOS and not be labeled as “physiologic adolescent anovulation”. The other major issue is the difference in the extent of defining hyperandrogenism based on the severity of hirsutism or acne.

### ***Implications of Early Diagnosis of PCOS***

The most common cause of female infertility is PCOS [7]. PCOS is a risk factor for metabolic syndrome and its consequences, decreased quality of life, and increased mortality [8]. Evidence suggests that early diagnosis and management play an essential role in preventing the complications of PCOS [9].

Overdiagnosis of PCOS has its perils. Studies have shown that adolescents with a diagnosis of PCOS are prone to depression and anxiety distress [10] and are worried about their chances of fertility and future morbidities [11]. It is the fear of the unknown, for the majority of the diagnosed PCOS patients are not satisfied with the information given by the health personnel regarding the disease. Diagnosis of PCOS may be delayed in 25% of the women by two or more years. The psychological impact on the PCOS woman could be due to the delay in the diagnosis and the disease itself [12]. Nevertheless, a correct and timely diagnosis of PCOS is needed at any stage of life the woman presents to the clinician.

### ***Clinical and Physical Features of PCOS in Adolescents***

History taking of the present illness with a focus on clinical symptoms, past medical history, details of puberty, menstrual history, social history, medical history, family history, and contraceptive use with the help of the attendee is helpful to diagnose PCOS and rule out ovulatory dysfunction and HA due to other factors. Long-standing, mild-to-moderate symptoms of androgen excess are usually due to PCOS. In contrast, rapid and frank virilization like a bulky muscle, increase in the size of the clitoris, and recession of temporal hair should raise concerns for the non-PCOS cause of hyperandrogenism.

Early pubarche or adrenarche is considered a marker of the later development of PCOS, although the pathology is not understood [13]. The documentation of the pattern of menstrual bleeding is the initial step in dealing with a suspected case of PCOS.

## Clinical Presentation of Polycystic Ovary Syndrome

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**Abstract:** Clinical presentation of PCOS varies among individuals. A patient with Polycystic Ovary Syndrome (PCOS) may present to the gynecologist with menstrual irregularities, mainly oligo-amenorrhea, by means of detected polycystic morphology on ultrasonography. A patient might also seek a dermatologist for hyperandrogenic manifestations, such as acne, hirsutism, androgenic alopecia, and acanthosis nigricans, or a fertility clinic with complains of infertility. Patients may arrive at the obesity clinic with metabolic abnormalities. Understanding the clinical features at presentation is crucial for understanding the disease and conducting a thorough assessment of the patient. Therefore, in this chapter, we will learn in detail about the assessment of all the clinical features of PCOS in detail. Since PCOS is the diagnosis of exclusion, clinical features differentiating PCOS from other conditions with overlapping symptoms like non-classical congenital adrenal hyperplasia, hypo-hyperthyroidism, hyperprolactinemia, Cushing syndrome, acromegaly, and ovarian and adrenal neoplasm will also be discussed.

**Keywords:** Acne, Adults, Adolescents, Alopecia, Clinical presentation, Diabetes mellitus, Ferriman Gallwey score, Hyperandrogenism, Hirsutism, Hyperandrogenaemia, Insulin resistance, Infertility, Lean polycystic ovary syndrome, Menstrual irregularities, Obese polycystic ovary syndrome, Oligomenorrhea, Polymenorrhea, Polycystic ovarian morphology, Phenotype.

### INTRODUCTION

The clinical manifestation of PCOS typically involves a constellation of symptoms of menstrual irregularities such as oligomenorrhea (infrequent periods) or amenorrhea (absence of periods), signs of hyperandrogenism, and polycystic ovaries [1, 2]. Furthermore, women with PCOS may experience infertility due to

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anovulation (lack of ovulation) or subfertility (difficulty conceiving) [3 - 5]. In addition to these primary symptoms, PCOS can additionally manifest through various anthropometric and systemic aberrations. These may include increased body weight or obesity, insulin resistance, dyslipidemia, and elevated blood pressure [6, 7]. PCOS has been associated with an increased risk for psychological disorders such as depression and anxiety [8, 9]. Therefore, a thorough clinical evaluation is necessary to assess the menstrual cyclicality, hyperandrogenism, and anthropometric and systemic abnormalities in women with suspected PCOS. Thus, a comprehensive evaluation of menstrual cyclicality, hyperandrogenism, and anthropometric and systemic abnormalities is necessary to properly diagnose and manage PCOS.

For a better understanding of presenting clinical features, in this chapter, we will discuss the cardinal features of menstrual irregularities, hyperandrogenism, polycystic ovarian morphology, and infertility. In the end, we will discuss anthropometric and metabolic features associated with PCOS.

### **Menstrual Cyclicality in PCOS**

The normal average menstrual cycle in women lasts for  $28 \pm 3$  days from the onset of the first day of menstruation to the first day of the commencement of the subsequent menstrual cycle [10]. The menstrual cycle is characterized by two distinct phases - the follicular phase and the luteal phase, with the proliferative phase being a component of the follicular phase. The follicular phase is variable in length and indicates folliculogenesis, while the luteal phase is relatively constant in duration, typically around 14 days, and is marked by progesterone production from corpus luteum, which prepares the endometrium for implantation [11]. Usually, a recurring monthly menstrual cycle indicates that ovulation is normal. Hence, irregular menstrual cycles are indicative of ovulatory dysfunction [12]. On the other hand, sometimes, women with regular menstrual cycles can also have ovarian dysfunction, which can be confirmed by measurement of serum progesterone levels [13]. In women with PCOS, menstrual cyclicality is often disrupted, manifesting as irregular or absent periods. The history of menstrual irregularity in PCOS starts with the onset of menarche. Oligomenorrhea is the most prevalent menstrual irregularity seen. However, some patients may have amenorrhea (absence of cycles for more than one year) or polymenorrhagia. Oligomenorrhea is a sign of oligo-ovulation and is defined by any of the following criteria [10]:

- Length of a menstrual cycle greater than 35 days.
- Total number of menstrual cycles less than 8 in a year.

Oligomenorrhea or amenorrhea is present in around 70-80% of women with PCOS. Women presenting with features of hyperandrogenism and claiming to be eumenorrheic actually have oligo-anovulatory cycles in 40% of cases. Menstrual irregularity is masked in patients taking oral contraceptive pills for hyperandrogenism. Oligo-amenorrhea indicates oligo-anovulation that results in infertility. Hence, PCOS is the chief cause of infertility and accounts for 90-95% of cases in infertility clinics. Polymenorrhea is the term used to describe a condition in which menstrual periods occur more frequently than usual, with intervals of less than 21 days between periods [10]. It is the opposite of oligomenorrhea. It is uncommon but not an exception in women with PCOS [14]. In adolescents, after menarche is achieved, the hypothalamic-pituitary-ovarian axis is still immature. Physiological maturation of the HPO axis occurs over the course of several years, and hence, it is not uncommon to get anovulatory and, thus, irregular cycles in early post-menarche years. Criteria for defining menstrual irregularity in adolescents are given in Table 1. Another criterion for defining menstrual irregularity in adolescents is a cycle length exceeding 90 days for any single cycle after more than one year post-menarche [15].

**Table 1. Definition of irregular menstrual cycles in adolescents.**

Post Menarche Duration	Definition of Irregular Menstrual Cycle
Less than 1 year	Irregular menstrual cycles are normal pubertal transition
1-3 year	< 21 or > 45 days
More than 3 years	< 21 or > 35 days or < 8 cycles per year

## Hyperandrogenism and PCOS

The normal function of androgens in women is to support bone mineral density, increase muscle mass, and facilitate sexual function. Testosterone, dihydrotestosterone, Dehydroepiandrosterone Sulphate (DHEA-S), Dehydroepiandrosterone (DHEA), and Androstenedione (ANS) are the main androgen forms in women. 50% of androgen biosynthesis occurs in the ovaries and adrenal gland (25% from each), and the rest of the 50% is derived from peripheral tissues. Testosterone is principally synthesized by the ovaries, androstenedione is synthesized equally by the ovaries and adrenal gland, and DHEAS is exclusively synthesized by the adrenal gland [14]. In PCOS, the majority of patients have hyperandrogenaemia, with ovaries acting as the primary source of excess testosterone production. Elevated free testosterone serves as a marker for diagnosis of PCOS. Most patients with PCOS are obese, and obesity leads to decreased SHBG levels, which may lead to elevated, low, or normal total testosterone levels and increased free unbound testosterone levels. It has been

## Cutaneous Manifestations of PCOS

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**Abstract:** Dermatological issues like hirsutism, acne, androgenetic alopecia, and acanthosis nigricans frequently coexist, significantly impacting patients' well-being. Understanding the underlying pathophysiological mechanisms is crucial for early detection and effective management. Key contributors to dermatological manifestations in PCOS include hyperandrogenism, insulin resistance, and chronic inflammation, mediated by immunological pathways, genetic predispositions, and hormonal imbalances. Hirsutism results from androgen excess and increased 5 $\alpha$ -reductase activity. Adult acne, influenced by androgens and follicular hyperkeratinization, worsens with chronic inflammation. Androgenetic alopecia involves complex mechanisms like Wnt signaling alterations and chronic scalp inflammation. Acanthosis nigricans, indicative of insulin resistance, highlights metabolic dysfunction in PCOS. Insulin-like growth factor receptor abnormalities and hyperinsulinemia drive its pathogenesis. This chapter draws the landscape of the interplay between endocrinology and dermatology in PCOS.

**Keywords:** Acanthosis nigricans, Androgenic alopecia, Acne vulgaris, Hirsutism.

### INTRODUCTION

A wide range of typical dermatological symptoms, including hirsutism, acne, Androgenetic Alopecia (AGA), Seborrheic Dermatitis (SD or seborrhea), and acne, are associated with PCOS [1]. These circumstances might manifest alone or in combination with additional virilization characteristics [2, 3]. The SAHA syndrome, often known as the tetrad of seborrhea, acne, hirsutism, and alopecia, is made up of the four previously listed diseases [4]. Furthermore, acrochordons, Demodex folliculorum, striae, xanthoma, psoriasis, pyoderma gangrenosum, acne, and hidradenitis suppurativa (PASH) syndrome have all been connected to PCOS.

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In addition, PCOS has been linked to two occurrences of mucosal pigmentation that may indicate Peutz-Jegher syndrome [5 - 8].

A robust association between dermatology and endocrinology emerges through immunological pathways primarily, as well as other contributing factors, elucidating numerous potential routes leading to cutaneous presentations in PCOS. The manifestation of skin conditions predominantly hinges on the PCOS phenotype, establishing a reciprocal relationship wherein they mutually influence each other, precipitating skin manifestations. While specific skin disorders are documented in PCOS patients, additional investigation is imperative to explore them comprehensively and elucidate the associated molecular mechanisms. Such insights can facilitate early detection and enhanced management strategies for PCOS.

### **Pathophysiology**

Studies on dermato-endocrinology have explored the association between PCOS and its skin-related symptoms. There is a possible pathogenic influence on modifications to metabolism [9]. Stressing dermatological characteristics in PCOS is essential for early identification, assisting in halting the development of extended after-effects [6, 10]. For example, studies by Botchkarev VA indicate that Bone Morphogenetic Protein (BMP) acts through a Mitogen-Activated Protein (MAP) kinase pathway to influence skin epidermal homeostasis and hair follicle growth in both the prenatal and postnatal stages [11]. Elevated levels of BMP were discovered in female PCOS patients in another investigation, suggesting that BMP has a role in reproductive abnormalities [12]. This calls into doubt the function of BMP in the cutaneous symptoms of PCOS and its applicability as an indication marker. The pathophysiology of PCOS in dermatology is influenced by immunology, genetic vulnerability, and hormonal abnormalities throughout metabolic pathways [6, 10].

Inflammation emerges as a fundamental mechanism underlying the various dermatological manifestations of Polycystic Ovary Syndrome (PCOS). This linkage underscores the intersection of immuno-dermatology and immune-metabolism, highlighting their intimate interconnection [12]. Key inflammatory proteins implicated in PCOS include C-Reactive Protein (CRP), Interleukin-18 (IL-18), Interleukin-6 (IL-6), and Tumor Necrosis Factor-Alpha (TNF $\alpha$ ) [13].

Cutaneous signs and symptoms of PCOS: In order to validate this correlation and provide more proof, a hormonal and histological analysis was carried out on rats with PCOS who were administered pentoxifylline, a drug having antioxidant and anti-tumor necrosing factor-alpha characteristics. The investigation found a strong relationship between changes in immunological markers and ovarian function,

clarifying the role of oxidative stress and chronic inflammatory pathways in PCOS [14]. The group of nuclear receptor subfamily 4 PCOS patients' ovaries express the orphan nuclear receptor family member 1 (NR4A1) gene, which is activated by transcription factors and androgens [15]. According to research by Murphy EP and Crean D, NR4A1 is essential in inflammatory situations because it inhibits inflammatory markers and regulates immune cell responses. Given the prevalence of hyperandrogenism in PCOS patients, NR4A1 is overexpressed in this population [16].

## **HIRSUTISM**

### **Definition**

Hirsutism refers to increased terminal hair growth in women within androgen-dependent regions. Traditionally, the validated modified Ferriman-Gallwey (mFG) score is utilized to assess hair growth across 9 androgen-dependent anatomical sites. A score of 8 or higher is conventionally required to characterize augmented hair growth as hirsutism. It is crucial to differentiate hirsutism from hypertrichosis, which denotes increased hair growth in androgen-independent regions [17].

### **Modified Ferriman-Gallwey Score**

The Modified FG score is a clinical method for quantifying terminal hair growth across 9 androgen-dependent body sites, graded from 0 to 4 based on hair density. The assessed sites include the upper lip, chin, chest, abdomen (upper and lower), back (upper and lower), arms, and thighs. Originally, the FG scoring also encompassed forearms and legs, which have been excluded due to their sensitivity to normal circulating androgens, potentially inflating the FG score unnecessarily. The final mFG score is the sum of individual site scores (with a maximum score of 36), with a threshold of 8 or higher indicating hirsutism (based on the 95th percentile value of scores among unselected women of reproductive age in most studies). However, this cutoff varies among different racial groups and can be as low as 3–5. Hirsutism severity is categorized as mild (8 to 16), moderate (17 to 25), and severe (26 to 36) based on the score [18].

### **Disadvantages of the mFG Score**

The mFG scoring system presents several drawbacks:

- Cumbersome, particularly during epidemiological studies.
- Intrusive, requiring patients to undress, which may lead to consent issues.
- Wide inter-observer variability.

**CHAPTER 7****Laboratory Assessment of Polycystic Ovary Syndrome****Lakshmi Nalini Kopalle<sup>1,\*</sup>**<sup>1</sup> *Ayan Institute of Medical Sciences, Moinabad, Telangana, India*

**Abstract:** Accumulating data indicates that the pathophysiology of PCOS may involve modified developmental and epigenetic programming brought on by hormonal dysregulation of the mother's uterine environment. In addition, there is a higher chance of PCOS-related metabolic and reproductive problems for both male and female relatives of PCOS-affected individuals. This review aims to provide an overview of the main research findings in the field of epigenetics and its influence on the manifestation of this disorder in women. The major focus will be DNA methylation studies, the role of miRNAs, and the transgenerational inheritance of PCOS.

**Keywords:** Androgen-secreting tumors, Cushing's syndrome, Hypothyroidism, Hyperprolactinemia, Non-classic congenital adrenal hyperplasia.

**INTRODUCTION**

Biochemical evaluation forms the crux of the diagnostic workup of PCOS. In the presence of clinical evidence of hyperandrogenism and irregular menstrual cycles, PCOS can be diagnosed only after excluding other causes that can result in similar clinical scenarios [2] as shown in Fig. (1). Additionally, the metabolic risk of PCOS needs to be evaluated. Tests are needed to exclude PCOS mimickers, which include hypothyroidism, hyperprolactinemia, Cushing's syndrome, Non-Classic Congenital Adrenal Hyperplasia (NCCAH), and androgen-secreting tumors [1 - 3]. It is prudent to test for Serum FSH and LH levels if menstrual irregularity progresses to or presents with amenorrhoea. In women who are sexually active, it is important to rule out pregnancy in the presence of amenorrhoea. The diagnosis of PCOS requires the fulfilment of Rotterdam criteria [2004]. Nevertheless, biochemical testing should not be limited to the same and must incorporate testing for dysmetabolism, especially dysglycemia and dyslipidemia.

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For ease of understanding, these tests can be grouped under the following categories:

- Tests to determine biochemical hyperandrogenism.
- Tests to establish ovulatory dysfunction.
- Test to exclude other causes.
- Tests to detect dysmetabolism.

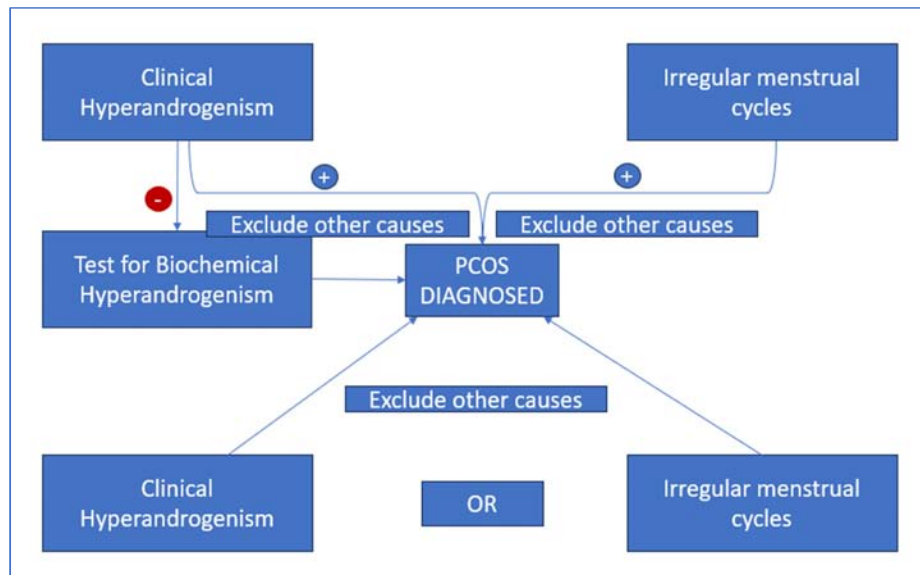


Fig. (1). Diagnostic algorithm of PCOS.

## How is Biochemical Hyperandrogenism Detected?

### *Testosterone -Total and Free*

Clinical assessment should go hand in glove with biochemical evaluation in the assessment of PCOS. Clinical hyperandrogenism is usually assessed by Modified Ferriman–Gallwey [mFG] scoring. A score of  $\geq 8$  is regarded as hirsutism. However, this assessment is not uniform across the races and carries with it a few limitations. In the presence of clinical hyperandrogenism, biochemical evaluation is usually not necessary [2]. Biochemical evidence becomes essential in the absence of clinical hyperandrogenism or if features are subtle. According to international evidence-based guidelines for the assessment and management of PCOS (2003), total and free testosterone are used to assess biochemical hyperandrogenism in the diagnosis of PCOS. Free testosterone should be assessed by equilibrium dialysis or ammonium sulfate precipitation. These two methods are cumbersome and expensive. Alternately, free testosterone can be estimated by

calculating the Free Androgen Index (FAI) [2]. FAI can be used as a proxy for the level of free testosterone. The ratio is the total testosterone level divided by the Sex Hormone Binding Globulin (SHBG) level and multiplied by 100, giving FAI. The concentrations of testosterone and SHBG are normally measured in nanomoles per liter. FAI has no unit.

**Liquid chromatography with tandem mass spectrometry (LC-MS/MS)** assay is highly accurate and is recommended [4, 5]. Direct free testosterone assays, such as enzyme-linked or radiometric assays, preferably should not be used in the assessment of biochemical hyperandrogenism in PCOS, as they have low sensitivity, accuracy, and precision. Reference ranges are specific to laboratories. For testosterone assay, the timing of sample collection is very important. The usual protocol involves blood sampling early morning, around 8.00 am, in a fasting condition. Biochemical hyperandrogenism cannot be reliably assessed in women on hormonal contraception due to effects on sex hormone-binding globulin and altered gonadotrophin-dependent androgen production. Withdrawal of OCPs for  $\geq 3$  months is needed with alternative options of contraception to evaluate for biochemical hyperandrogenism [2]. An overtly high testosterone level usually points towards an alternate diagnosis [2]. Only in rare situations of most severe PCOS (Ovarian Hyperthecosis), serum total testosterone may be higher than 2ng/mL.

#### ***Androstenedione and Dehydroepiandrosterone Sulphate***

If serum testosterone is not elevated, then androstenedione and Dehydroepiandrosterone Sulfate (DHEAS) can be measured, but these are less specific and have a limited role in hyperandrogenism of ovarian origin. Ideally, androstenedione and DHEAS should be measured using LC-MS/MS. Though these compounds are usually elevated in hyperandrogenism due to adrenal causes, serum DHEAS levels may increase [up to 8mg/L] in half of the patients with PCOS [6, 7]. Despite the almost exclusive adrenal production of DHEAS, this rise in PCOS remains unexplained.

#### **Tests to Establish Ovulatory Dysfunction**

As mentioned in the original Rotterdam criteria and the 2018 International PCOS Guideline, ovulatory dysfunction is a key diagnostic feature of PCOS with irregular menstrual cycles [2, 8]. Nevertheless, ovulatory dysfunction can occur with regular menstrual cycles. When anovulation needs to be confirmed, hormonal assessment becomes essential, especially if PCOS is clinically suspected and cycles are regular. Serum progesterone assessment can aid in the identification of ovulatory dysfunction in women suspected of PCOS with regular menstrual cycles [9]. Polycystic Ovarian Morphology (PCOM) serves as a proxy

## Imaging in Polycystic Ovary Syndrome

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**Abstract:** PCOS has historically been diagnosed clinically, often supported by laboratory parameters. However, the role of ultrasound has evolved over time. While initially used to identify features consistent with PCOS, its interpretation has become more complex. The presence of a “string of pearls” appearance on ultrasound has contributed to the perception of PCOS, but this may not always accurately reflect the condition. Advancements in ultrasound technology, particularly with higher frequency probes and endovaginal imaging, have improved the visualization of ovarian structures. However, there is inconsistency in how ultrasound findings are interpreted by clinicians and understood by patients. The presence of multifollicular ovaries, often observed on ultrasound, is frequently associated with PCOS, yet the significance of this finding in relation to the different PCOS phenotypes remains uncertain.

**Keywords:** PCOS, Pulsatility index, Resistivity index, Vascularization index.

### INTRODUCTION

Ultrasound is the primary imaging modality performed on a patient suspected to have PCOS. However, it is only a part of the diagnostic criteria and not mandatory for all women to undergo ultrasound. According to the diagnostic algorithm proposed in the international evidence-based guidelines of 2023, ultrasound is only recommended for adults and is not essential for the diagnosis; it may even be replaced with serum AMH levels (Table 1).

Ultrasound is readily available, devoid of ionizing radiation, and an easily repeatable investigation. It is recommended that in all acceptable scenarios, a transvaginal ultrasound be performed. The following features are used to make a diagnosis of polycystic ovarian morphology on ultrasound:

- Follicle number per ovary (FNPO):  $\geq 20$  in at least one ovary.
- Follicle number per section (FNPS):  $\geq 10$  in either ovary.
- Ovarian volume (OV):  $\geq 10$  ml in either ovary.

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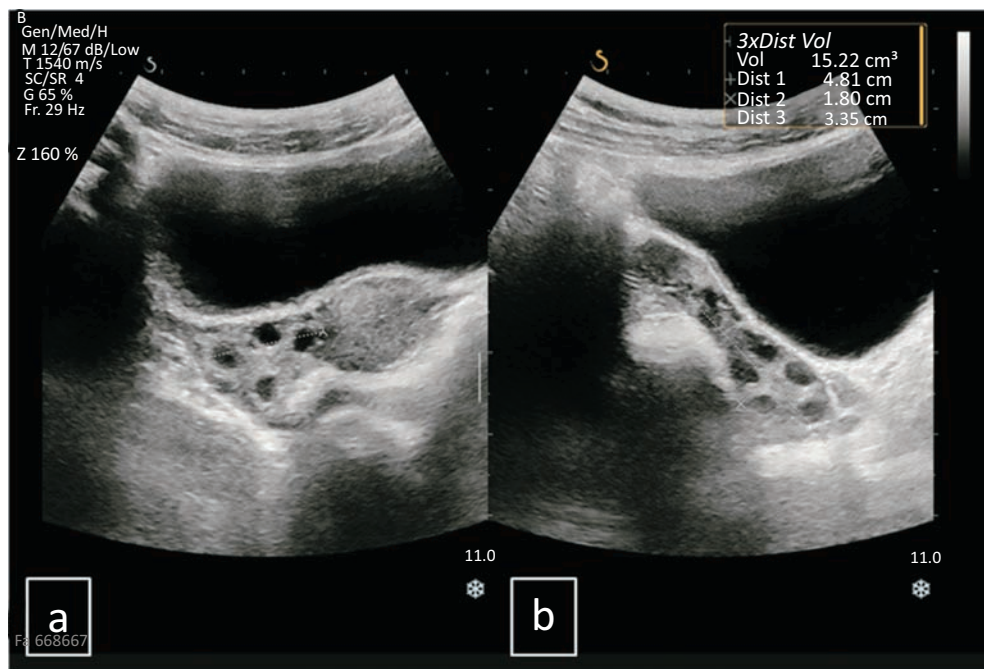
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PCOM is based on follicle excess (FNPO, FNPS) and/or ovarian volume.

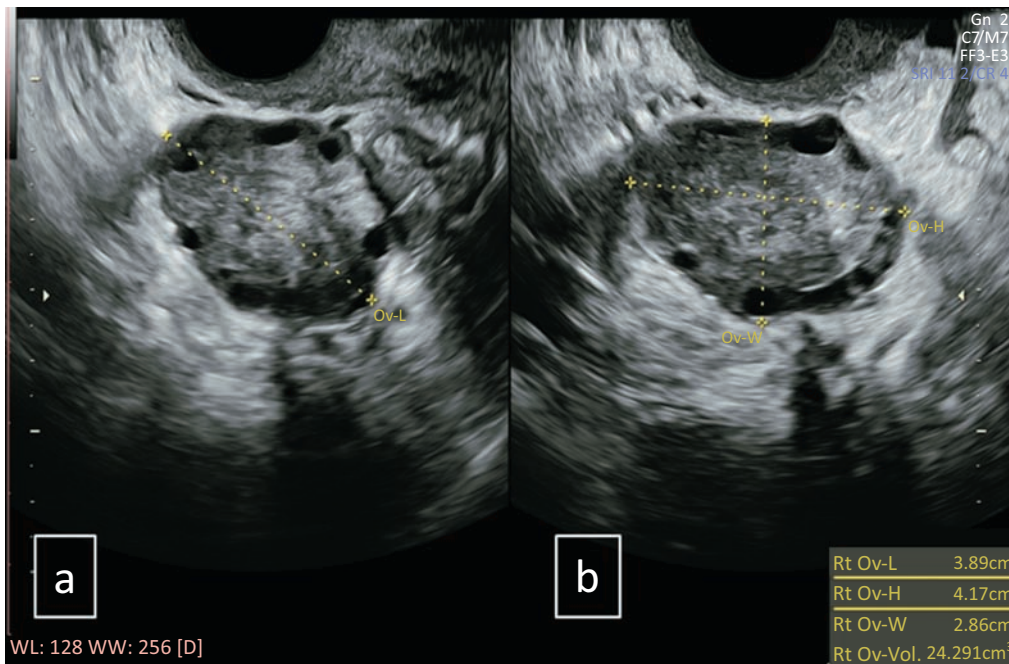
If a transvaginal ultrasound cannot be performed, then FNPS and/or ovarian volume should be assessed on a transabdominal ultrasound. The presence of a dominant follicle or a corpus luteal cyst should prompt evaluation of the contralateral ovary [1, 2].

### Ovarian Volume

The threshold volume considered for the diagnosis of PCOM is 10 ml in either ovary (Figs. 1 and 2). The formula used for volume calculation is a simplified ellipsoid model ( $0.5 \times \text{length} \times \text{width} \times \text{thickness}$ ). Length and width are measured in the longitudinal plane, and thickness is measured in the orthogonal plane. The bladder should be adequately filled for a transabdominal scan; an overfilled bladder can potentially compress the ovaries and prevent accurate volume measurement [3 - 9].



**Fig. (1).** Transverse (a) and sagittal oblique (b) views of a transabdominal USG show a bulky right ovary with a volume of 15.2 cc.



**Fig. (2).** Transvaginal ultrasound showing bulky ovary with multiple follicles; FNPO was more than 20 (not shown), and the ovarian volume was 24.22 cc.

### **Follicular Excess**

If a transvaginal ultrasound is performed, FNPO is a better indicator of follicular excess and requires the presence of at least 20 follicles in either ovary. This criterion requires a thorough examination of both ovaries to count every single follicle accurately. These follicles or “cysts” represent the follicles that have failed to mature and suffered growth arrest. When a transabdominal scan is performed, it is understood that comprehensive evaluation of the entire ovary may be difficult, and thus, the number of follicles in a particular section is counted and considered significant when there are at least 10 in either ovary [2].

### **Magnetic Resonance Imaging MRI**

MRI is not routinely indicated or performed in patients suspected to have PCOS. It is not a part of the diagnostic criteria because ultrasound can adequately assess ovaries. Nevertheless, if performed in unequivocal cases where a transabdominal approach is insufficient and a transvaginal scan is not an option, MRI can show features similar to ultrasound. On T2-weighted images, small, peripherally arranged hyperintense cysts can be seen. Additionally, these patients also show an abundance of ovarian stroma, which is seen as a central hypointensity within the

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**CHAPTER 9**

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**Role of Hyperandrogenism in PCOS Pathogenesis****Faria Afsana<sup>1,\*</sup>**<sup>1</sup> *Department of Endocrinology, BIRDEM General Hospital, Dhaka, Bangladesh*

**Abstract:** Hyperandrogenism in PCOS contributed from ovary and adrenal glands clinically manifests as hirsutism, acne, and alopecia. In PCOS, LH hypersecretion over FSH occurs due to increased frequency of pulsatile secretion of gonadotropin-releasing hormone. In contrast to an associated deficiency in FSH, excess LH promotes ovarian androgen production, or FSH resistance harms follicular development. In PCOS women, LH:FSH ratio alteration leads to ovarian theca cell proliferation, which leads to elevated steroidogenesis and, eventually, hyperandrogenism. There are 5 types of androgen in women: Dehydroepiandrosterone Sulfate (DHEAS), Androstenedione (A4), Testosterone (T), Dehydroepiandrosterone (DHEA), and Dihydrotestosterone (DHT). Among these androgens, testosterone and DHT are more active than others. Androgen is also secreted from the adrenal gland in small amounts. By the enzyme aromatase, testosterone converts to estradiol, both of which coordinate the function of reproductive function in women. Excess of androgen from the ovary causes ovarian follicular changes, leading to anovulation and menstrual irregularities. Not only the development but the progression of PCOS is also influenced by hyperandrogenism. Complications of PCOS, such as type 2 diabetes, hypertension, and obesity, also occur by hyperandrogenism, increasing insulin resistance. Thus, it is important to address this hyperandrogenism clinically to stop the progression and complications of PCOS.

**Keywords:** Hyperandrogenemia, Insulin resistance, Lifestyle modifications, Metformin, Nonalcoholic fatty liver disease, Polycystic ovary syndrome.

**INTRODUCTION**

Hyperandrogenism, irregular ovulation, and enlarged multifollicular ovaries are the hallmarks of PCOS. Additionally, women who have PCOS are more likely to have non-communicable diseases caused by insulin resistance, such as Type 2 Diabetes Mellitus (T2DM), cardiovascular diseases, psychological disorders, infertility, and endometrial and ovarian cancer as age advances [1, 2]. In PCOS, hyperandrogenism is contributed by excess androgen from the ovary and adrenal

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gland and is the key driving force in the growth of signs/symptoms and complications. Hyperandrogenism, the important criterion for diagnosis, is found in 60%-80% of women with PCOS [3]. Excess androgen leads to ovulatory disorder in the form of anovulation, menstrual irregularities, hirsutism, and acne, arguing that hyperandrogenism triggers PCOS problems in addition to its clinical manifestations but is also an important risk factor. In PCOS, abnormalities in the increased pulse frequency of GnRH stimulate LH and FSH secretion from the pituitary gland. A relative deficiency in FSH function hinders follicular development and growth, whereas an excess of LH boosts ovarian androgen production. In PCOS women, an imbalance between LH and FSH promotes ovarian theca cell development, leading to elevated steroidogenesis and hyperandrogenism. This chapter will emphasize the pathophysiological events that hyperandrogenism may have a consequence on PCOS development [4].

### Androgen in Women

In women, LH from ovarian theca cells stimulates the secretion of androgens from cholesterol, and a small amount of androgen is secreted from the zona reticularis of the adrenal gland through the stimulation of Adrenocorticotrophic Hormone (ACTH). Additionally, a small amount of androgen is generated in peripheral tissues by conversion [5]. Women of different ethnic backgrounds have different forms of androgens: 1. Androstenedione (A4), 2. Testosterone (T) 3. Dehydroepiandrosterone sulfate (DHEAS), 4. Dihydrotestosterone (DHT), 5. Dehydroepiandrosterone (DHEA) [6]. Sources of these are described in Table 1. Sturdy androgens, such as DHT and testosterone, bind to the Androgen Receptor (AR) directly to produce biological effects. On the other hand, DHEAS, DHEA, and A4 are the major androgen precursors remaining in blood in higher proportions than DHT and T but with lower biological effects.

**Table 1. Type and source of androgen in women (Dehydroepiandrosterone sulfate (DHEAS), Androstenedione (A4), Testosterone (T), Dehydroepiandrosterone (DHEA), Dihydrotestosterone (DHT).**

Androgen	Source
DHEAS	Adrenal zona reticularis (100%)
DHEA	Adrenal zona reticularis (50%) Conversion from DHEAS in circulation (30%) Ovaries (20%)
A4	Adrenal gland (50%) Ovary (50%)
T	Adrenal zona fasciculata (50%) Ovary (50%)

(Table 1) cont....

Androgen	Source
DHT	In the surrounding tissue (such as the liver, adipose tissue, and the pilosebaceous unit) [from T by 5 $\alpha$ -reductase (5 $\alpha$ RD)] Adrenal zona fasciculata (little quantity)

In the ovary, theca cells use 17 $\beta$ -hydroxysteroid dehydrogenase to convert A4 to testosterone, oestrone, and Cytochrome P450 Aromatase (CYP19A1) in the granulosa cells. Finally, 17 $\beta$ -hydroxysteroid dehydrogenase converts estrogen to oestradiol. In peripheral tissue, testosterone is converted to Estradiol (E) by aromatase, and both T and E coordinate female reproductive endocrine system balance and function. In women, androgen in peripheral organs increases muscle mass, calcium deposition, and bone growth [7], responsible for adrenarche (appearance of pubic and axillary hair) and female sexual desire. Excess androgen causes ovarian follicular dysplasia, impairing ovulation and resulting in menstrual irregularities. Thus, sustaining the equilibrium between androgen production and secretion is essential to maintain normal ovulatory function.

### Hyperandrogenism in PCOS

Hyperandrogenism contributes to producing the symptoms of PCOS as well as potentiates the development of metabolic consequences. It is established that in women with PCOS, excessive androgen is primarily produced by the ovary and very little amount by the adrenal gland. As adrenal androgen contributes very little to hyperandrogenism in women, it is the ovarian source of hyperandrogenism that produces the features of PCOS and causes metabolic disorders among them. There is another school of thought that the pathophysiology of PCOS may have a crucial source at the pituitary level due to the addition of estrogen with a relative FSH insensitivity, which limits FSH release. The increased testosterone level decreases the potential of progesterone and oestradiol to reduce the hypothalamic GnRH pulse frequency [8]. Thus, losing weight in obese people lowers insulin, testosterone, and estrogen levels, restores normal gonadotropin output, and regulates menstrual cycles in PCOS-affected women.

Symptoms of PCOS are mainly irregular menstruation in the form of prolongation and alteration of the duration of the menstrual cycle, amenorrhea due to anovulation, and even endometrial carcinogenesis. Acne and hirsutism are the other two features of PCOS contributed by hyperandrogenism. On imaging, especially on pelvic ultrasonogram, there may be a presence of immature antral follicles (at least 12) throughout the whole ovary and/or a volume of more than 10 milliliters. Though this imaging finding is not a mandatory diagnostic criterion for PCOS and produces a dilemma in diagnosing adolescents and young adults, the

**CHAPTER 10****Insulin Resistance in the Pathophysiology of Polycystic Ovary Syndrome****Sindhuja Reddy Chada<sup>1</sup> and Rakesh Kumar Sahay<sup>1,\*</sup>**<sup>1</sup> Department of Endocrinology, Osmania Medical College, Hyderabad, India

**Abstract:** In addition to reproductive abnormalities, metabolic imbalances, especially insulin resistance, characterize the core of PCOS pathology that, in turn, heightens the existing hormonal dysregulation and possibly culminates in long-term complications like type 2 diabetes and cardiovascular disorders. Insulin resistance is seen in most people with PCOS. Insulin resistance in PCOS is due to post-receptor signaling defects and is selective with attenuated metabolic and normal mitogenic pathways. It is also probably tissue-selective. Insulin resistance alters the hypothalamic-pituitary-ovarian axis and increases LH production greater than FSH. LH increases androgen production from thecal cells of the ovary. Insulin resistance increases the risk of impaired glucose tolerance, type 2 diabetes mellitus, obesity, cardiovascular disease, and dyslipidemia. So, strategies for decreasing insulin resistance are important. Lifestyle intervention and insulin sensitizers are in use in clinical practice for improving insulin sensitivity. Further research is needed to develop newer therapeutics for insulin resistance.

**Keywords:** AMH, Androgen, Estrogen, FSH, Feedback, GnRH, Galanin, GABA, HPO, Hyperandrogenism, Insulin, Kisspeptin, LH, Leptin, Neurons, Ovarian, Opioid, PCOS, Progesterone, Secretion.

**INTRODUCTION**

The pathogenesis of PCOS is complex and multifactorial, including genetic, environmental, and transgenerational components. These sources drive the underpinnings of unbalanced hypothalamus-pituitary-ovarian axis signaling, promoting ovarian and adrenal hyperandrogenism [1 - 5]. This is worsened by hyperandrogenism-related adipose tissue accumulation and dysfunction with lipotoxicity and oxidative stress [6 - 8].

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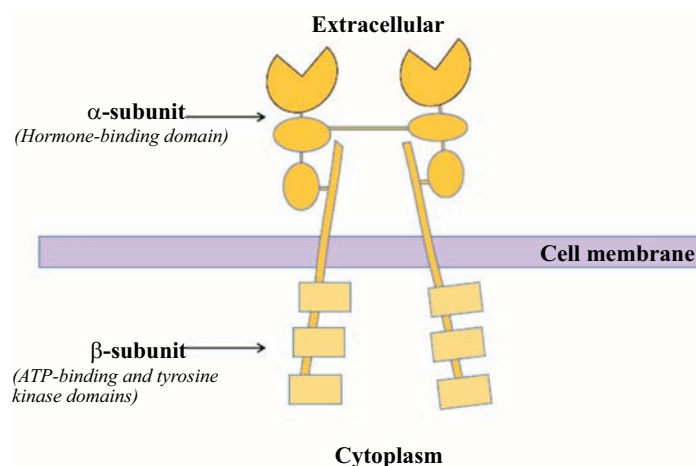
PCOS women with insulin resistance and hyperinsulinemia have higher CVD risk [2]. Insulin resistance is seen in up to 95% of obese people with PCOS and in up to 75% of lean PCOS women [9]. In this chapter, we will discuss the role of insulin signaling and resistance in the pathophysiology of PCOS.

### **Insulin-Mediated Signaling Pathway**

It is an intracytoplasmic signaling system that regulates the body's development, survival, and metabolism. It involves many processes, the first of which is the binding of insulin to insulin receptors and Insulin-Like Growth Factors (IGF). Insulin Receptor Substrate (IRS), Src Homology 2 Domain-Containing (SHC), Growth Factor Receptor-Bound Protein 2 (GRB) [2], SH2B Adapter Protein 2/Adapter Protein with a PH and SH2 domain (SH2B2/APS), and Insulin Receptor Substrate (IRS) are among the substrates to which the insulin receptor binds in the second step. Numerous signal transduction pathways for proliferation and physiological processes are activated by this interaction [10].

### **Insulin Receptor**

The insulin receptor is a tetrameric protein that consists of 2 extracellular  $\alpha$  subunits and 2 transmembrane  $\beta$  subunits that are joined by disulfide bonds as shown in Fig. (1). The binding of insulin with IR causes a conformational shift, leading the  $\beta$  subunits' kinase activity to be initiated, allowing the recruitment of substrates for receptors. The best characteristic of these is IRS (Insulin Receptor Substrate) [10]. Metabolic and mitogenic signals make up the two components of downstream signaling following IR activation.



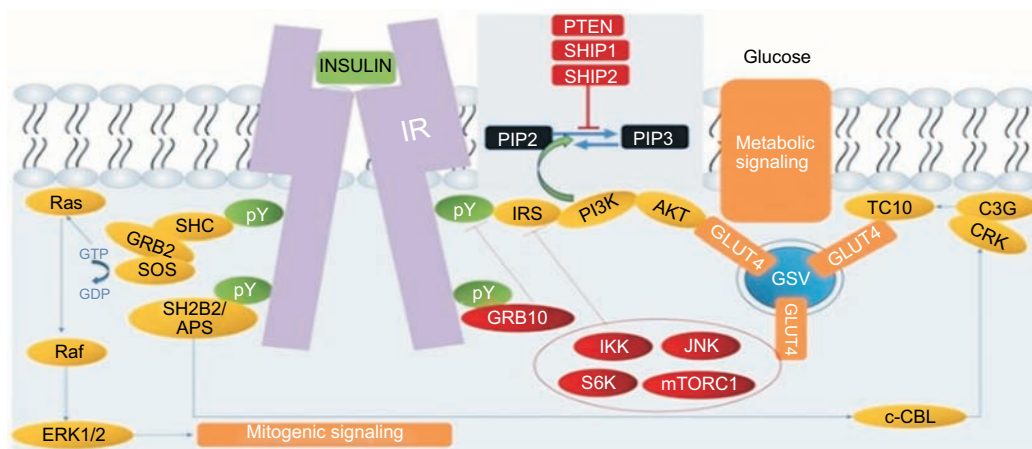
**Fig. (1).** Insulin receptor.

### Metabolic Pathway of Insulin Signaling

PI3-kinase (PI3K) and Akt pathways are the key pathways bridging IRS proteins to the metabolic actions of insulin. Activation of Akt leads to phosphorylation and activation of many downstream targets [11]. The expression of lipogenic and gluconeogenic genes is regulated by the Foxo family. Akt phosphorylates Foxo and causes the elimination of Foxo from the nucleus, thus impeding its transcriptional activity [12]. Akt also phosphorylates and inactivates glycogen synthase kinase 3, resulting in glycogen synthase activation and glycogen accumulation in the liver [13]. The potential of PGC-1 $\alpha$  to stimulate gluconeogenesis and fatty acid oxidation is reduced by Akt-dependent phosphorylation of PGC-1 $\alpha$  [14].

### Mitogenic Pathway of Insulin Signaling

A second branch of the insulin/IGF-1 signaling pathway with a role in mitogenic signals is the Grb2-SOS-Ras-MAPK pathway, which is activated without relying on the PI3K/Akt pathway as shown in Fig. (2). This plays a part in cell proliferation or differentiation, modulating gene expression or cytoplasmic events, such as cytoskeletal reformation [10].



**Fig. (2).** Insulin signaling. Any anomalous signal has the potential to significantly alter tumorigenesis and metabolism. It is therefore essential to quickly halt the insulin signal at varied gradations. Serine/threonine phosphatases, such as PP1 and PP2, comprising PP2A, PP2B and PP2C, are examples of phosphoprotein phosphatases that negatively regulate insulin signaling.

### Negative Regulators of Insulin

Control over insulin signaling is constant because any anomalous signal has the potential to significantly alter tumorigenesis and metabolism. It is, therefore,

## Adipocyte Dysfunction and its Role in PCOS Pathophysiology

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**Abstract:** The pathogenesis of Polycystic Ovary Syndrome (PCOS) is mostly dependent on adipocyte malfunction, which contributes to the syndrome's diverse metabolic and reproductive symptoms. The main cells of adipose tissue, called adipocytes, are not just passive energy stores; they are also active endocrine organs that secrete a variety of adipokines, hormones, and inflammatory mediators that regulate metabolism. Adipose tissue inflammation, insulin resistance, and dysregulated adipokine production are all signs of adipocyte dysfunction in PCOS, which exacerbates the metabolic abnormalities that are typical of the condition.

**Keywords:** Adipocytes, Adipose dysfunction, Adipsin, Adiponectin.

### INTRODUCTION

Adipocyte dysfunction has emerged as a significant contributor to PCOS pathophysiology. In states of nutrient excess, adipocytes tend to enlarge (hypertrophy) or it can lead to the formation of new adipocytes (hyperplasia). The adipocyte hypertrophy establishes a microenvironment characterized by pro-inflammatory cytokine secretion, hypoxia, and increased free fatty acids in the circulation. This leads to insulin resistance [1 - 3].

### THE ADIPOSE TISSUES' ROLE IN PCOS

The adipose tissue's role in PCOS Triacylglycerols (TAGs), which are energy-storing molecules, is a recognized function of adipose tissue. Insulin sensitivity in adipocytes is quite high. This promotes the absorption of glucose. Additionally, it modifies lipid metabolism by causing triacylglycerides to accumulate more and their breakdown inside adipocytes to decrease. Metabolic diseases can arise from any disturbance of any function. As of right now, the secretory roles of adipocytes

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are well understood. Numerous endocrine hormones are produced in substantial amounts from adipocytes. It has been observed that obesity lowers the amount of adiponectin, a serine protease that is released by adipocytes [4]. Leptin is among the most significant of them. It is crucial to the control of body weight because it serves as an afferent “adipostat” signal of fat mass to central brain centers. Additionally, it exerts peripheral effects that control the metabolism of glucose. The *ob* gene is the source of the hormone leptin. “Leptos” is the Greek word for thin. Food intake is suppressed, and energy expenditure is increased by central leptin signaling. Conversely, a lack of leptin decreases feelings of fullness. Leptin functions as a messenger for energy storage. The development of leptin resistance in obesity disrupts the negative feedback loop of increased energy availability and the suppression of food intake. The pathophysiology of PCOS and the involvement of adipocyte dysfunction affect the brain's ability to access body fat and regulate fat storage [5].

### **Adiponectin**

People with obesity have lower levels of adiponectin than lean people. It possesses anti-inflammatory and anti-atherogenic properties. It is a desirable therapeutic target for the treatment of obesity and insulin resistance since it also controls blood glucose levels. However, therapy aimed against adiponectin function is still being studied. Adiponectin inhibits the synthesis of malonyl-CoA and increases fatty acid oxidation *via* activating AMP-activated Kinase (AMPK). In different tissues, adiponectin can have either an autocrine or paracrine effect. The liver, skeletal muscle, and heart are thought to be the primary locations of adiponectin activity. Adiponectin has pronounced effects that make insulin more sensitive. The liver and muscle have provided the most complete mechanistic characterizations of these [6]. Adiponectin reduces the plasma glucose by inhibiting hepatic glucose production. It has been described that the genetic deletion of adiponectin has impaired hepatic insulin sensitivity. Thiazolidinediones (TZDs) increase insulin sensitivity by increasing adiponectin levels. Low plasma adiponectin levels are associated with the progression of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. As a result, adiponectin protects the liver and averts metabolic disorders. In those in good health, up to 80% of insulin-mediated glucose absorption occurs in skeletal muscle [7]. Adiponectin can increase insulin sensitivity, which in turn can facilitate the absorption of glucose by the skeletal muscle.

Additionally, cardioprotection and low circulating levels of adiponectin are associated with coronary artery disease.

## **Resistin**

Insulin resistance is induced by resistin. Two recognized receptors that resistin interacts with include Toll-Like Receptor 4 (TLR4) and Adenylyl Cyclase-Associated Protein 1 (CAP1). The expression of chemokines and the recruitment of monocytes are both influenced by resistin signaling *via* these receptors. It causes inflammatory reactions that eventually contribute to atherosclerosis. Resistin controls blood glucose levels while fasting. There have been reports of elevated circulating resistance in obese people. Reduced insulin-mediated glucose absorption in the liver is also linked to elevated resistin levels. The increased levels of resistin are associated with systemic lupus erythematosus, inflammatory bowel disease, and rheumatoid arthritis [8].

## **Omentin-1**

Omentin-1 is mainly expressed in visceral adipose tissue, intestine, and lungs. It is also expressed in the ovaries. Omentin -1 levels are negatively correlated with the levels of free testosterone. Thus, the elevated free testosterone in PCOS patients reduces the levels of protective omentin-1. This adipokine is a potential PCOS biomarker. Insulin resistance is associated with lower levels of plasma omentin-1 in PCOS independent of BMI status. There is a downregulation of omentin-1 gene expression in insulin-resistant PCOS patients. The lower omentin-1 levels are associated with higher circulating TNF alpha and other cytokines in the inflammatory state.

## **OBESITY AND PCOS**

It has been found that fat increases androgen production. Sex Hormone-Binding Globulin (SHBG) levels are lowered in obese women as a result of hyperinsulinemia. Women who are overweight are more likely to experience reproductive problems. Infertility and irregular menstrual periods are more prevalent in obese women than in normal-weight individuals. The relative risk of anovulatory infertility rises proportionately with BMI in women of reproductive age [9]. Women with PCOS are exposed to elevated testosterone levels over extended periods of time. This might alter these women's distribution of body fat. Compared to women without PCOS, who typically store fat in the lower part of the body (gynoid), they will have a higher distribution of fat in the upper area of the body (android). Insulin resistance is brought on by the central distribution of fat [10]. Increased waist circumference and waist-hip ratio in comparison to BMI-matched control women are indicators of upper-body obesity. In PCOS, adipose tissue is a metabolically active, complex tissue made up of many different types of interdependent cells. Adipose tissue adapts preadipocyte development into

## Hypothalamic-Pituitary-Ovarian Axis and its Disarray in PCOS

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**Abstract:** Hypothalamic-Pituitary-Ovarian (HPO) axis dysfunction lies central to the pathophysiology of this condition. The cyclicity of the HPO axis is maintained by rigorous feedback mechanisms—both positive and negative. In PCOS, altered hypothalamic kisspeptin signaling culminates in increased LH secretion, leading to increased androgen output from the ovarian theca cells and impaired FSH secretion, leading to aberrant folliculogenesis. A number of factors may be responsible for this hypothalamic-pituitary-ovarian disarray, like Anti-Mullerian Hormone (AMH), insulin, Insulin-like Growth Factor- 1 and 2 (IGF-1 & IGF-2), leptin, galanin, *etc.* Also, various neurotransmitters like opioid signaling, GABAergic, and glutamatergic transmission may act in tandem with the causation of this endocrine disorder. Still, many questions remain unanswered for which extensive research is being undertaken.

**Keywords:** Androgen, AMH, Estrogen, FSH, Feedback, Galanin, GABA, GnRH, Hyperandrogenism, HPO, Insulin, Kisspeptin, LH, Leptin, Neurons, Ovarian, Opioid, Progesterone, PCOS, Secretion.

### INTRODUCTION

The female reproductive cycle seems to have an intricate interplay between neuromodulatory inputs as well as peripheral signals. Any deviation from this delicate mechanism causes disarray in the entire physiology. Polycystic Ovarian Syndrome (PCOS) is a common reproductive endocrine disorder that involves perturbation of this endocrine axis as well as metabolic derangements. It is associated with hirsutism, oligo/amenorrhoea, anovulation, infertility, Polycystic Ovarian Morphology (PCOM), as well as an increased propensity to develop metabolic illnesses like diabetes, hypertension, *etc.*, and in some cases, cancer. Although the exact pathophysiology is yet to be demystified, the disorder of the

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hypothalamic-pituitary-ovarian axis in tandem with insulin resistance is understood to be one of the main contributors.

## NORMAL PHYSIOLOGY

Cyclicity of the female Hypothalamic-Pituitary-Ovarian-axis (HPO axis) is maintained by the GnRH (Gonadotropin-Releasing Hormone) pulse generator located in the hypothalamus; this also plays a vital role in initiating puberty and maintaining gonadal function. It is the amplitude and pulsatility of the GnRH secretion that decides the pattern of release of the gonadotropins.

However, recent studies point towards the importance of Kisspeptin. Kisspeptin is an upstream regulator of the GnRH neurons in the hypothalamus and acts through a G-protein-coupled receptor 54, *i.e.*, GPR-54, also known as KISS1R. The location of kisspeptin neurons differs between humans and rodents. In rodents, it was found in the arcuate nucleus and anteroventral periventricular nucleus (AVPV) extending into the periventricular nucleus [1]. In humans, kisspeptin neurons are predominantly distributed in the infundibular nucleus and sparsely in the preoptic nucleus [2]. Paracrine and autocrine signaling mediated by various factors leads to the modulation of kisspeptin action. It has been recently discovered that kisspeptin secreted from the posterodorsal subnucleus of medial amygdala influences the hypothalamic kisspeptin secretion aided by GABA and glutamatergic neurotransmission. This kisspeptinergic output from the amygdala, in turn, increases the GnRH pulse frequency [3].

GnRH leads to the secretion of the two gonadotropins, FSH (Follicle Stimulating Hormone) and LH (Luteinising Hormone), from the anterior pituitary, and both act on the gonad (ovary in the female). FSH helps in the later development of follicles in ovaries and also modulates the aromatization of androgens to estrogens. LH, although classically described for its role in the luteal phase for sustaining progesterone secretion, has a role during the follicular phase as well, augmenting androgen synthesis from theca cells (for subsequent aromatization to estrogen in granulosa cells), initiating oocyte maturation from the mid-cycle, and also leading to ovulation. High frequency of release of GnRH pulses leads to increased synthesis of  $\beta$ -subunit of LH through the activation of Steroidogenic Factor-1 (SF-1) and Early Growth Response 1 (EGR1) transcription factors as well as the repression of FSH  $\beta$ -subunit. Conversely, low-frequency release of GnRH leads to a reverse effect, *i.e.*, increased synthesis of FSH  $\beta$  subunit through the Activator Protein-1 (AP-1) transcription family [4 - 8].

Ovarian steroidogenesis employs two cell lines in the ovary to work in tandem. LH leads to the synthesis of androstenedione from its precursor, cholesterol, in Theca Cells (TC) in a dose-dependent manner through a number of enzymatic

steps mediated by CYP11A1, CYP17, and HSD3B2 [9]. Granulosa Cells (GC) convert the androstenedione to estrogen by aromatization under stimulation by FSH. Some paracrine factors secreted by oocytes, like-Bone Morphogenetic Protein-15 (BMP-15) and Growth Differentiation Factor 9 (GDF-9), regulate follicle formation [10, 11]. Also, Insulin-like Growth Factors (IGF), activin, inhibin, *etc.*, are autocrine/paracrine regulators of hormonal function in the ovary [12].

### **Feedback Mechanisms**

GnRH release from hypothalamic neurons is controlled by a number of central and peripheral signals, some of which are stimulatory (Kisspeptin, Norepinephrine, and Neuropeptide Y) and some are inhibitory (Endogenous Opioids, Interleukin-1, Progesterone, *etc.*). GnRH also may control its own secretion through an ultra-short feedback loop [13]. Also, the secretion of GnRH is subject to negative and positive feedback cycles. For example, it has been shown that various doses of estrogen could stimulate LH surge both in humans and primates [14]. On the other hand, it was also found that estrogen and progesterone from the ovary lead to the inhibition of pituitary gonadotropin synthesis, with the differences heavily dependent on dose in a time-dependent manner. For example, estradiol led to suppression of GnRH pulse amplitude, and progesterone led to suppression of pulse frequency. In particular, progesterone was more able to acutely suppress the release of GnRH and LH, along with the action on its receptor in the hypothalamic kisspeptinergic outflow [15 - 18]. However, the progesterone-mediated suppression would occur *via* two mechanisms. The first is the nuclear transmembrane receptor requiring gene transcription, thereby being slower. Another type of faster progesterone-mediated inhibition does not involve gene transcription [19].

Kisspeptin neurons also get suppressed by this progesterone-mediated feedback. Also, fine-tuning of the kisspeptin output of Kisspeptin/Neurokinin B/Dynorphin (KNDy) neurons in the hypothalamus takes place through the stimulatory NKB pathway and inhibitory dynorphin pathway, which are co-expressed together in the arcuate nucleus of hypothalamus [20]. Also, FSH-mediated synthesis of inhibin and activin leads to the regulation of FSH secretion through inhibition and activation, as apparent from the names.

Regarding the positive feedback mediated by estrogen in the follicular phase, the mechanism of the same has been enigmatic for long. ER $\beta$  receptors have been identified in some neurons of GnRH as well as kisspeptin neurons but not ER $\alpha$ .

## Familial Aggregation and Contribution of Various Genes in PCOS

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**Abstract:** PCOS is proposed to be an orchestration of gene-gene and gene-environment interactions. The syndrome is highly inherited, and the risk increases by up to 40% in families with a history of PCOS. Familial clustering of PCOS symptoms is now well documented, pointing to the genetic contribution to the condition. Research currently available indicates that PCOS is a complex illness influenced by a number of variables, including environment, lifestyle, diet, genetics, and epigenetics. Nevertheless, it is currently unknown how much of each component contributes to the total phenotype. Currently, no single gene or related genes have been unanimously regarded as a significant cause of PCOS. Several genes have been linked to PCOS, and mutations or polymorphisms in these genes have a role in disease development. Until now, accurate genetic variations in PCOS have not been documented. Single-gene mutations, on the other hand, cause the phenotypic manifestations of PCOS. This chapter discusses the several genetic aspects linked to PCOS through gonadotropin regulation, gonadotrophin activity, ovarian and adrenal steroidogenesis, steroid hormone activities, energy homeostasis, insulin action, insulin secretion, and chronic inflammation.

**Keywords:** Candidate gene biology, GWAS, Identical twins, Transgenerational impact.

### INTRODUCTION

Literature has sufficient evidence that PCOS clusters in families and both genetic and environmental factors contribute to this disorder [1 - 5]. A twin study from The Dutch Twin Register database estimated 70% heritability influence of genetic factors on PCOS [6]; however, GWAS have identified less than 10% of PCOS heritability. This indicates the contribution of epigenetic factors as well in the

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pathogenesis of PCOS. Genome-wide Association Studies (GWAS) from the recent past have supported oligogenic/polygenic inheritance of PCOS similar to type 2 diabetes and cardiovascular diseases [7]. Elucidating the type of inheritance has been difficult due to incomplete penetrance and epigenetic modifications [5]. Mitochondrial DNA heritability may be another contributing factor to the genetic lineage of PCOS [8]. There are now three manually constructed and published genetic databases for PCOS: PCOSKBR2 (2020), PCOSBase (2017), and PCOSDB (2016). Table 1 presents a comparison of the three databases [9 - 11].

**Table 1. Comparison of the three PCOS databases.**

Attributes	PCOSKBR2 (2020)	PCOSBase (2017)	PCOSDB (2016)
<b>Name</b>	Polycystic Ovary Syndrome KnowledgeBase	Polycystic Ovary Syndrome Base	Polycystic Ovary Syndrome Database
<b>URL</b>	<a href="http://www.pcoskb.bicnirrh.res.in/">http://www.pcoskb.bicnirrh.res.in/</a>	<a href="http://pcosbase.org/">http://pcosbase.org/</a>	<a href="http://www.pcosdb.net">http://www.pcosdb.net</a>
<b>Content</b>	Content 1237 illnesses linked to PCOS, 533 genes, 145 SNPs, 29 miRNAs, and 1150 09362457 pathways. An additional 4023 genes found in microarray expression studies on PCOS are also included ( <a href="http://pcosbase.org/">http://pcosbase.org/</a> )	There are additionally 8185 PCOS-related proteins, 7936 domains, 1004 pathways, 1928 disorders linked to PCOS, 29 disease classifications, and 91 tissues included.	Database for Polycystic Ovary Syndrome:46 correlated phenotypes, 427 molecular changes with thorough annotations, and 208 genes.

Screening of the whole genome in search for candidate genes in multifactorial diseases like PCOS is not fruitful. In such a disease, case-control studies on large population size and Genome-Wide Association Studies (GWAS) are more useful to find probable associations. GWAS studies are helpful in deciphering the genetic loci that are associated with disease traits. These genetic loci are either directly involved (if they are near or in the gene) or they may be involved in genetic upregulations or downregulations. In this context, GWAS studies provide a more comprehensive approach to identifying the genetic basis of PCOS.

Various GWAS studies (Chinese, European, and Korean) have been performed to detect around 19 different genetic loci associated with PCOS [12 - 18]. Candidate gene studies are used to validate GWAS study findings by identifying the Single Nucleotide Polymorphisms (SNP) contributing to the molecular etiopathogenesis of PCOS [13, 19]. The various genetic studies undertaken and the genes identified in Asian ancestry are highlighted in Table 2 below.

**Table 2. Genetic studies and identified genes in PCOS patients.**

Type of Study	Identified Genes in Asian Ancestry
Gene polymorphisms associated with PCOS in case control studies [5-7, 20-22]	GnRHR, FSHR, FTO, IR, IRS
Mapped genes in GWAS [23]	YAP1, RAB5B, SUOX, LHCGR, THADA, DENND1A, FSHR, HMGA2, TOX3, INSR, C9orf3
Genotype-phenotype associated studies [21]	THADA, DENND1A- associated with endocrine and metabolic disturbances and PCOS LHCGR and INSR associated with anovulation C9orf3 associated with all classical PCOS features
Pathway analysis studies using datasets obtained from GWAS [20, 23-29]	INS, GNAQ, PLCB3, STXBP1, SMC3, PLCB2, PLCZ1- associated with oocyte meiosis and the regulation of insulin secretion

## PREVALENCE

According to reports, PCOS affects between 5 and 20% of women in their reproductive years globally [5]. The incidence of PCOS among women in India who are of reproductive age reportedly ranges from 3.7% to 22.5% [30, 31]. According to Bharali *et al.*'s comprehensive review and meta-analysis, the pooled prevalence of PCOS in Indian women was 5.8% according to NIH criteria, 10% according to Rotterdam's criteria, and 10% according to AES criteria [32].

## GENETIC PATHWAYS AND CANDIDATE GENES LINKED TO PCOS

Various ethnic and academic organizations have conducted independent investigations and they have identified many potential genes or loci associated with PCOS. The majority of these putative genes fall into one of the six main categories or pathways. A few key genes for each category/pathway are listed in Table 3:

**Table 3. Genetic variations associated with PCOS.**

S. No.	Variants Associated with PCOS	Genes	Cytogenetic Location	References
1	Genes involved in steroid hormone effect	1. Androgen Receptor Gene ( <i>AR</i> ) 2. Sex Hormone-Binding Globulin Gene ( <i>SHBG</i> )	Chromosome Xq12 Chromosome 17p13-p12	[33]
2	Genes involved in gonadotropin action and regulation	1. Follicular-Stimulating Hormone Receptor ( <i>FSHR</i> ) 2. Anti-Müllerian Hormone ( <i>AMH</i> )	Chromosome 2p16.3 Chromosome 19q13.3	[34]

**CHAPTER 14****Role of Epigenetics in Painting the Landscape of PCOS****Mona Sharma<sup>1,\*</sup>, Aayushi Taneja<sup>1</sup>, Nandana Devi<sup>1</sup> and Ashutosh Halder<sup>1</sup>**<sup>1</sup> *Department of Reproductive Biology, AIIMS, New Delhi, India*

**Abstract:** Accumulating data indicates that the pathophysiology of PCOS may involve modified developmental and epigenetic programming brought on by hormonal dysregulation of the mother's uterine environment. In addition, there is a higher chance of PCOS-related metabolic and reproductive problems for both male and female relatives of PCOS-affected individuals. This Chapter aims to provide an overview of the main research findings in the field of epigenetics and its influence on the manifestation of this disorder in women. The major focus will be DNA methylation studies, the role of miRNAs, and the transgenerational inheritance of PCOS.

**Keywords:** DNA methylation, Epigenetics, MicroRNAs, PCOS, Transgenerational impact.

**INTRODUCTION**

Due to the variance in phenotypic expression among individuals and within family lineages, epigenetic changes have been proposed as the root cause of PCOS [1 - 3]. Many have noted that genetics, environment, intrauterine, and infancy history all play important roles in the development of PCOS [4,5]. It is still up for debate, nevertheless, to what extent genetic, epigenetic, and environmental variables actually contribute to this disease.

It is interesting how epigenetics plays a part in PCOS. The term “epigenetics” refers to the modification of the expression of particular genes without actually altering the DNA sequence. Epigenetics involves methylation, which is the addition of methyl (-CH<sub>3</sub>) groups to the fifth carbon atom of the pyrimidine ring of a cytosine followed by a guanine, known as CpG dinucleotides (CpGs), the existence of microRNAs (miRNAs), and the histones post-translational modifications [6]. While not affecting genotype, epigenetic events have the

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potential to be transmissible and have an impact on phenotype. More specifically, DNA methylation typically results in the inactivation and/or dysregulation of transcription of a specific gene, with varying outcomes based on whether the expression of that gene is advantageous or detrimental for a given condition [7 - 9].

Hyperandrogenism is considered to be the primary cause of PCOS, despite the fact that phenotypes associated with the condition vary greatly. Preventative and targeted treatments are desperately needed because current PCOS treatment options are only able to partially reduce symptoms. The syndrome's three primary clinical characteristics are clinical or biochemical hyperandrogenism, polycystic ovarian morphology (PCOM), oligo-ovulation, or anovulation with irregular menstruation.

In order to diagnose PCOS, at least two of these three clinical symptoms must be present, according to the most recent evidence-based International Guidelines for the Assessment and Management of PCOS. There are thus four distinct phenotypes of PCOS: phenotype A, which includes hyperandrogenism, ovulatory dysfunction, and PCOM; phenotype B, which includes hyperandrogenism and ovulatory dysfunction exclusively; phenotype C, which includes hyperandrogenism and PCOM; and, lastly, phenotype D, which includes ovulatory dysfunction and PCOM. In an unselected population, phenotypes A and B together account for 40–45% of cases, while phenotypes C and D account for around 35% and 20% of cases, respectively. Those with hyperandrogenism (A–C) are regarded as the most severe of these traits [10 - 12].

Geographic and racial disparities in PCOS prevalence are not supported by data, yet women who are very obese are more likely to have PCOS (up to >25%), and having comorbid obesity exacerbates all PCOS symptoms. Inconsistent data makes it difficult to diagnose PCOS in teenage girls [13]. A diagnosis of PCOS should not be made until more than two years after menarche, according to the most recent evidence-based guidelines from the International Consortium. It also necessitates the presence of both irregular or absent ovulatory menstrual cycles and clinical and/or biochemical hyperandrogenism [14].

Recent studies have shown the role of Antimüllerian Hormone (AMH) and Dihydrotestosterone (DHT) as potential biomarkers for PCOS diagnosis [15, 16]. Significant metabolic abnormalities such as dyslipidemia, insulin resistance, and hyperinsulinemia are related to PCOS and raise the risk of Type 2 Diabetes Mellitus (T2DM), cardiovascular disease, and gynecological malignancies [17 - 23]. Anxiety, depression, and autism spectrum disorders are among the neuropsych-

hiatric illnesses that women with PCOS are more likely to develop [24 - 27]. Moreover, PCOS is also considered heritable.

### **Epigenetics: DNA Methylation**

DNA methylation is linked to transcriptional repression and genomic imprinting and can be found in CpG islands, gene bodies (including exons and introns, that is, the gene region from transcription start to stop sites), imprinting regulatory regions, and transposable elements. It is interesting to note that the development of PCOS may be influenced by the methylation of multiple genes related to reproductive function, ovarian steroidogenesis (*e.g.*, genes encoding for aromatase, peroxisome proliferator-activated receptor gamma 1 (PPAR $\gamma$ 1), glucose and lipid metabolism, adipose tissue activity, inflammation, and immune response regulation [28 - 32]. A study conducted recently by Echiburù *et al.* examined DNA methylation in the promoter regions of genes encoding for leptin (LEP), leptin receptor (LEPR), adiponectin (ADIPOQ), adiponectin receptor 1 and 2 (ADIPOR1 and ADIPOR2), AMH, and AR in 24 newborns (2–3 months old) of PCOS-affected women (12 treated with metformin during pregnancy), as well as 24 newborns of subjects without PCOS [31]. They found out that daughters of women with PCOS differed in one CpG site in the promoter region of LEPR and two in LEP, as well as one in ADIPOR2 and two in AR.

Remarkably, Sagvekar *et al.* proposed several other differentially methylated genes (DMGs) as novel epigenetic candidates for mediating ovarian dysfunction. These DMGs mainly contribute to hyperandrogenism and oocyte development defects. Examples of these genes include Resistin (RETN), Calcium-Sensing Receptor (CASR), Growth Hormone Releasing Hormone Receptor (GHRHR), Aldo-Keto Reductase Family 1 member C3 (AKR1C3), Aldo-Keto Reductase Family 1 member C3 (AKR1C3), Growth Hormone Releasing Hormone Receptor (GHRHR), and Tumor Necrosis Factor (TNF) [32].

DNMT3A and DNMT3B are the two main *de novo* DNA methylation enzymes in mammals [33, 34]. DNMT3L is required for maternal genomic imprinting and is expressed only in the germline. DNMT3L does not have any catalytic activity by itself, but it interacts with DNMT3A and DNMT3B to perform the methyltransferase function [35]. There is also *de novo* methylation activity in DNMT3C. Silencing of the most current and harmful retrotransposons is its specialized function during fetal spermatogenesis [36]. In essence, genomic stability is ensured by DNA methylation.

In contrast, demethylation of DNA is done by three methylcytosine dioxygenases (TET1–TET3) *via* the oxidation of methylcytosine wherein 5-methylcytosine is gradually converted to 5-hydroxymethylcytosine, 5-hydroxymethylcytosine, and

## Oxidative Stress and Inflammatory Status in PCOS

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**Abstract:** Polycystic Ovary Syndrome (PCOS) stands out as one of the most common endocrine and metabolic disorders, showcasing a range of clinical symptoms like polycystic ovaries, heightened androgen production, irregular menstrual cycles, ovulation irregularities, infertility, and pregnancy complications. Furthermore, it has been linked to chronic low-grade inflammation. The development of PCOS involves multiple factors, and among them, Oxidative Stress (OS) and low-grade chronic inflammation play a crucial role. These two factors have a profound influence on the normal functioning of reproductive organs, particularly in terms of follicular development and the pathogenesis of PCOS. The abnormal function of Reactive Oxygen Species (ROS) and inflammatory markers directly affects the progression of PCOS and its impact on reproductive health. Patients with PCOS exhibit notably higher levels of oxidative stress markers and inflammatory markers compared to healthy individuals, suggesting a relationship between elevated oxidative stress and the progression of PCOS. This chapter provides an overview of significant oxidative markers and inflammatory molecules associated with PCOS, particularly in the context of coexisting conditions such as obesity, insulin resistance, and hyperandrogenism. Additionally, the potential implications of oxidative stress on immune function are briefly addressed.

**Keywords:** CVD, Catalase, Glutathione peroxidase activity, Homocysteine, Insulin resistance, Inflammation, Low-grade inflammation, Lipid peroxidation, Malondialdehyde, Oxidative stress, Obesity, Polycystic ovarian syndrome, PCOS, Reactive oxygen species, Superoxide dismutase.

### INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is the most common endocrine and metabolic disorder that causes female infertility, affecting 6% to 19% of women of reproductive age with variance among race and ethnicity [1]. PCOS is characterized by heterogeneous clinical manifestations such as polycystic ovaries, increasing androgen secretion, oligo-ovulation, menstrual irregularity, infertility,

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and pregnancy complications. Women with PCOS demonstrate abnormal menstrual cycles, infertility, insulin resistance, increased risk for type 2 diabetes mellitus, coronary heart disease, atherogenic dyslipidemia, cerebrovascular morbidity, anxiety and depression, and a higher risk of developing endometrial or ovarian cancer pathophysiology [2]. The etiology of PCOS is still unknown. Insulin resistance and hyperandrogenism are hallmarks of PCOS and are likewise connected to metabolic dysfunctions and heightened production of proinflammatory and coagulatory markers that add to its basic pathophysiology [3]. It is currently certain that insulin resistance and hyperandrogenism apply a proinflammatory state in PCOS and are liable for the development of chronic low-grade inflammation, a consequence of metabolic aberration and ovarian dysfunction [4]. PCOS is strongly linked to hyperandrogenism and mild systemic and ovarian chronic inflammation, with Oxidative Stress (OS) being identified as a potential contributor to the development of PCOS. It has been observed that OS levels rise during inflammation, further reinforcing the association between hyperandrogenism, inflammation, and PCOS [5]. In this chapter, we will explore the possible interplay of oxidative stress and inflammation in PCOS.

### **Oxidative Stress in PCOS**

Oxidative Stress (OS) was initially introduced as a concept in redox biology and medicine in the year 1985 [6]. Oxidative stress is considered to be an oxidative and antioxidant imbalance caused by surplus oxidant production [7]. Oxidants are chemical elements that generally gain electrons by losing a positive charge. They are formed as a result of regular cellular metabolism, including Reactive Oxygen Species (ROS) and reactive nitrogen species derived from Nitric Oxide (RNS). ROS are produced from molecular oxygen and consist of oxygen ions, free radicals, and peroxides. The oxidation of NADPH by a membrane-bound NADPH oxidase leads to the production of superoxide. The role of ROS is significant in various biological processes, including the regulation of redox-sensitive transcription factors, signaling pathways, killing of invading pathogens, interaction with diverse molecules, wound healing, and tissue repair processes. Small quantities of ROS are usually produced during oxygen metabolism and effectively neutralized by an antioxidant defense system, which comprises various enzymes such as superoxide dismutase, catalase, peroxidase, glutathione peroxidase, glutathione reductase, and thioredoxin reductase, as well as endogenous, dietary antioxidant molecules and non-enzymatic antioxidant systems, such as reduced thiols, vitamins C and E, and catecholamines [8]. An increase in ROS levels can also be triggered by various oxidative stressors like exposure to Ultraviolet (UV) radiation, smoking, alcohol consumption, utilization of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), and other external agents. Infections, as well as various inflammatory processes, can likewise prompt

expanded degrees of ROS. Redox signaling and oxidative stress have a significant impact on the regular balance of cells, which in turn plays a crucial role in the development of various diseases. These disturbances also affect key ovarian processes, including meiosis, ovulation, and corpus luteum maintenance. As a result, the essential development of mature oocytes and eggs is impeded, contributing to the progression of PCOS [9]. It has been over two decades since the pioneering studies were conducted, which provided evidence of elevated levels of OS and a decrease in antioxidant capacity in women diagnosed with PCOS [10]. Multiple pathways in the ovary contribute to the production of ROS, with mitochondria playing a key role in generating ROS through respiratory electron transfer systems in oocytes. The Endoplasmic Reticulum (ER) serves as a key location for protein synthesis and a primary generator of ROS. The accumulation of misfolded proteins induces ER stress, which in turn triggers a massive release of  $\text{Ca}^{2+}$  into the mitochondria. This disruption of regular mitochondrial ROS levels leads to an elevation in  $\text{O}_2^{\bullet-}$  [9].

In the context of PCOS, the generation of OS is caused by synchronized metabolic aberration, like hyperandrogenism, hyperinsulinemia, obesity, and dyslipidemia, which play a key role in the pathogenesis of PCOS. The presence of excessive androgens originating from the ovaries and/or adrenal glands, either during prenatal development or early in life, can lead to the development of abdominal adiposity and android obesity. These conditions contribute to hypoadiponectinemia and dysfunction in adipose tissue. Additionally, the excessive release of cytokines at both local and systemic levels results in oxidative stress [11, 12]. Abdominal adiposity can lead to higher androgen levels, either directly through the response of the ovaries and adrenals to inflammation or indirectly by causing insulin resistance and increased insulin production. This increased insulin then prompts the glands to produce more androgens [13]. The presence of OS, in addition to other etiologic mechanisms, contributes to the manifestation of PCOS.

Several indicators of oxidative stress include homocysteine, malondialdehyde (MDA), and Asymmetric Dimethylarginine (ADMA). Endogenous antioxidants include the antioxidative enzymes and the nonenzymatic antioxidants, which play a crucial role in maintaining intracellular redox homeostasis. Antioxidative enzymes include Paraoxonase-1 (PON1), Glutathione Peroxidase (GPx), Superoxide Dismutase (SOD), and catalase. Non-enzymatic antioxidants include  $\alpha$ -tocopherol (vitamin E), ascorbic acid (vitamin C), ferritin, albumin, glutathione,  $\beta$ -carotene and other carotenoids, phenolics, flavonoids, and phenolic acids that play a pivotal role in the regulation of OS.

## CHAPTER 16

## Endocrine Disruptors and Polycystic Ovary Syndrome: How Strong are the Links?

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**Abstract:** The U.S. Environmental Protection Agency (EPA) defines EDC as “an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process”. The global production of EDCs increased 23.5 fold between 1947 and 2007. In 2012 alone, around 9.5 trillion pounds of pesticides, chemicals, drugs, and plastics were produced. The most common contaminants are BPA(bisphenol-A), pesticides, and CPF (chlorpyrifos). Substantial evidence from *in vitro* and animal studies incriminates many of these endocrine disruptors in the induction of reproductive and metabolic aberrations resembling PCOS characteristics. This chapter describes the differential diagnosis strategies for the accurate identification of PCOS in these intricate scenarios.

**Keywords:** Adolescents, Diagnosis, Menopause, Pregnancy, PCOS.

### INTRODUCTION

Endocrine disruptors, also known as Endocrine-Disrupting Chemicals (EDCs), are hormonally active chemical compounds that “interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for development, behaviour, fertility, and maintenance of homeostasis” [1 - 3]. The term EDC was introduced in 1991 at the Wingspread Conference Center in Wisconsin conference named “Chemically-induced alterations in sexual development: The wildlife/human connection”. Long-term, uninterrupted exposure to this group of agents not only leads to malignancy but also interferes with growth and reproduction.

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Since the exact mechanism by which EDCs create health hazards is not clearly known, only those that are strongly proven as harmful are banned, *i.e.*, diethylstilbestrol. However, these hormonally active agents slowly and silently cause endocrine, metabolic, and immunological malfunctions in our body, leading to multiple disorders. While more than 1,000 EDCs are currently known, some of the common harmful EDCs are:

- **Bisphenol A (BPA)** is used in hard plastics like bottles, food containers, toys, and plastic home and kitchen appliances.
- **Dichlorodiphenyltrichloroethane (DDT)** and its derivatives (banned in most countries).
- **Polychlorinated Biphenyls (PCBs)** are now banned.
- **Phthalates** are used in beauty products and plastic wares.
- **Triclosan** is used as an antibacterial product [4].
- Some naturally occurring **phytoestrogens** [5].

### **Health Hazards Related to EDCs**

EDCs enter our body mainly through the oro-nasal and transdermal routes. Fetuses and neonates are more sensitive to EDCs compared to adults. EDCs mainly affect sex steroid metabolism in adults, leading to subfertility and hormone-sensitive cancers. EDCs also interfere with energy metabolism and cause obesity, insulin resistance, Type 2 Diabetes (T2D), and thyroid dysfunction. In neonates and children, EDCs may affect brain development [6].

### **Endocrine Disruptors and Metabolic Disorders**

EDCs trigger metabolic reprogramming by interfering with receptor-ligand interaction, disrupting appetite regulation, energy expenditure, and metabolic rate. BPAs can be orexigenic and lead to obesity. Intrauterine BPA exposure in rodents leads to obesity, heart diseases, early puberty, and insulin resistance in adult life.

DDT, a well-known pesticide, is reported to cause insulin resistance. Of note, countries like South Africa and India, still using DDTs, have a higher number of people suffering from T2D compared to most of the countries that banned DDT [7].

A study from Denmark reported that children exposed to EDC –PFC (poly fluoro carbon) and PCBs (Polychlorinated biphenyls) found in industrial waste may acquire a higher propensity to develop NAFLD [Recent terminology: metabolic dysfunction-associated steatotic liver disease (MASLD)] [8].

Transgenerational exposure to multiple EDCs at very low doses during early development stages promotes obesity and related complications. Besides interfering with endocrine signaling, EDCs can disrupt adipocyte differentiation, function, and metabolic processes [9]. Lipophilic EDCs act as obesogens, leading to increased fat deposition in the adipose tissue [10]; PCBs and Dioxins are two major groups of obesogenic EDCs [11]. Tributyltin chloride and triphenyltin chloride, two well-known Organotins (Organic pollutants, a group of EDCs), are reported to act as nanomolar agonist ligands for both retinoid X receptors and Peroxisome Proliferator-Activated Receptors (PPARs). These receptors are crucial in lipid homeostasis and adipogenesis [12]. Thus, activating them inappropriately may lead to obesity and problems regarding lipid metabolism. Which in turn may cause problems of insulin resistance and metabolic disorders.

EDCs induce insulin resistance and alter insulin-mediated glucose uptake. Angle *et al.* 2013 showed that adiponectin level decreases with constant exposure to BPA in a mouse model [13]. In their illustrative review, Rotondo and Chiarelli showed environmental pollutants affect pancreatic  $\beta$ -cell function, survival, and insulin release. BPAs have been shown to cause glucose intolerance, T2D, and fatty liver in mice [14].

### ***Endocrine Disruptors and Subfertility***

It is long established that EDCs play a significant role in increasing male fertility-related issues. In their extensive meta-regression on Sperm Concentration (SC) and Total Sperm Count (TSC), Levine *et al.* reported a 59.3% decline in TSC between 1973 and 2011 in Europe, North America, New Zealand, and Australia [15]. In their study, Hond *et al.* 2015 showed that urinary levels of two well-known EDCs, phthalates and triclosan, in 163 male subjects were negatively associated with inhibin-B and positively with LH, indicating that subjects having higher concentrations of these EDCs in their urine had a higher chance of reproductive dysfunction. Urinary levels of bisphenol-A also negatively correlated with testosterone levels [16].

It is reported that cryptorchidism, hypospadias, oligospermia, and testicular cancer arising from disturbed prenatal testicular development can be a result of exposure to a given EDC (or a mixture) at a particular period over time. In the case of females, EDCs have been proposed for disorders. These disorders include abnormal ovulation and lactation, breast cancer, benign breast disease, uterine fibroids, endometriosis, T-shaped uteri, and abnormal oviductal anatomy. In both males and females, EDCs play a crucial role in infertility. PCBs, phytoestrogens, fungicides, pesticides, and other xenobiotics can disrupt brain-sexual dimorphism.

## Gut and Vaginal Microbiome Dysbiosis in PCOS

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**Abstract:** Recent research shows a possible causative relationship of PCOS pathogenies with gut and vaginal dysbiosis. Reduction in ( $\alpha$ ) diversity and modification in beta ( $\beta$ ) diversity and relative abundance of taxa of gut and vaginal microbiome is well known among PCOS women. Gut dysbiosis results in leaky gut and endotoxemia, which lead to chronic inflammation, insulin resistance, and hyperandrogenism with metabolic and reproductive PCOS phenotype. Altered microbial metabolites such as Short-Chain Fatty Acids (SCFA), Branch-Chain Amino Acids (BCAA), and Bile Acids (BA) contribute to the pathogenesis of PCOS. The gut-brain axis is also contributed mainly through the modification of gut peptide hormones. The interplay between gut dysbiosis and Hyperandrogenism (HA) is bidirectional. The understanding of this link between microbial dysbiosis has opened new therapeutic opportunities in PCOS.

**Keywords:** Bile acids, Gut-brain axis, Gut microbiome, Vaginal microbiome, Short chain fatty acids.

### INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is an endocrine and metabolic disorder with clinical features of androgen excess, which is predominantly seen in women at reproductive years. Its prevalence is around 10% in women in the reproductive age group globally, and most females have insulin resistance, obesity, dyslipidemia, hyperandrogenism, and ovulatory dysfunction [1 - 3]. Heterogeneity in clinical features and lack of therapeutic response to treatment have made PCOS one of the most challenging diseases to manage. Pathogenesis of PCOS is yet to be fully understood, although understanding its pathogenesis would be the key to the successful management of these patients. Among the causative factors, genetic factors play a main role, and recent studies indicate an association

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between gut and vaginal microbiota, which has led many interest scholars to dig deeper into the unknown [4, 5]. The human gut microbiome consists of about  $10^{13}$  and  $10^{14}$  microorganisms, and among these microorganisms, more than 1000 different kinds of species and more than 7000 different kinds of strains are classified as bacteria (bacteriome), viruses (virome), fungi (fungome), archaea (archaeome), and few protozoal parasites [6]. The vaginal microbiome is in healthy dynamic balance throughout the reproductive life of a female under the regulation of estrogen and progesterone. There is a complex and subtle balance between the human host and its microbial inhabitants to maintain the health of humans. Microbiome has become a research hotspot in exploring new therapeutic modalities for malignancy, immune diseases, and metabolic diseases [7, 8]. There is current evidence to suggest that gut and vaginal microbial dysbiosis of PCOS women is related to the pathogenesis of hyperandrogenism, chronic inflammation, insulin resistance, and metabolic syndrome through many mechanisms and may affect the clinical phenotype and complications of PCOS [4, 9].

### **Gut and Vaginal Microbial Composition in PCOS**

Over the last decade, several leading studies have demonstrated gut and vaginal microbial dysbiosis in terms of decreased alpha ( $\alpha$ ) diversity and change in beta ( $\beta$ ) diversity in both women with PCOS [9 - 11] and in PCOS-like rodent models created using treatment with letrozole or dihydrotestosterone (DHT) [12, 13]. A recent study on obese PCOS adolescents from diverse ethnic backgrounds also showed similar gut microbial dysbiosis, suggesting that microbial changes occur by adolescence like other manifestations of PCOS [14]. Alpha diversity estimates the species richness and/or evenness of a community, implying its overall health, while beta diversity represents how similar or different the composition of one gut microbial community is compared to another community. These changes are known to be associated with immunological and metabolic disorders [15]. In addition, it has been shown that the relative abundance of different microbial taxa has been altered in PCOS rats compared to healthy rats [15]. To maintain a balanced microenvironment, including the microbiota, regular menstrual cycles with adequate levels of estrogen and progesterone will be necessary to induce physiological changes in the reproductive tract's epidermal cells. However, those with PCOS will experience irregular menstruation, which will cause fluctuations in the lower vaginal tract microbiomes' composition. This would lead to numerous unfavorable reproductive consequences, including infertility and abortion [16]. Changes in microbial composition in women with PCOS compared to healthy adult females have been demonstrated in studies, see Fig. (1) [17]. Therapeutic targets for dysbiosis have come to the limelight as the knowledge of microbiome increases. In interventional studies and clinical trials of Fecal Microbiota Transplantation (FMT), supplementation of probiotics and traditional Chinese

medicine had been used to regulate gut microbiota as a therapeutic intervention for certain diseases including PCOS.

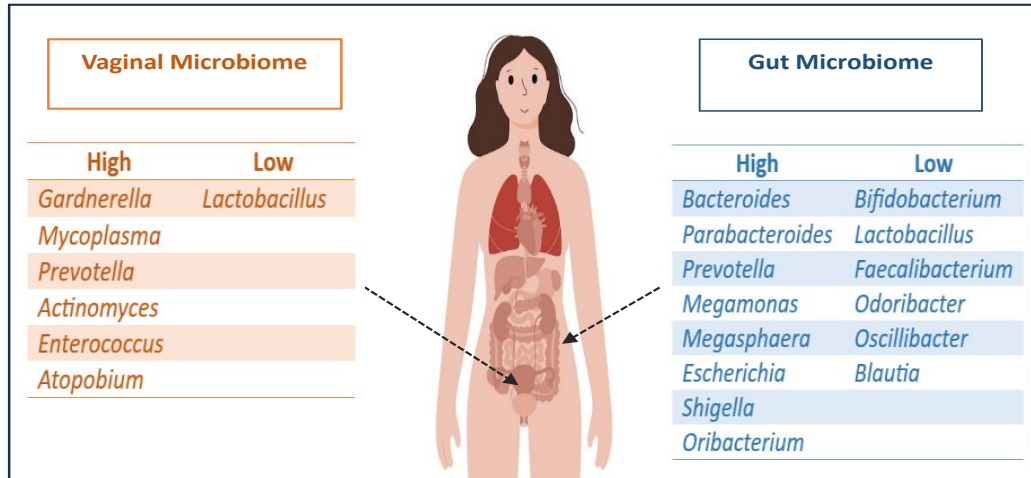


Fig. (1). Microbial composition of women with PCOS.

### Intersection Between Gut and Vaginal Dysbiosis and PCOS

The exact pathogenesis behind PCOS is not known; however, several genetic, immunological, and metabolic pathways have been postulated. There are several hypotheses that describe the pathophysiological relationship between gut dysbiosis and hyperandrogenic PCOS. According to the DOGMA hypothesis proposed by Tremellen and Pearce in 2012, “Dysbiosis of Gut Microbiota” can trigger a chronic inflammatory response through the activation of the immune system, which leads to insulin receptor dysfunction and Insulin Resistance (IR). The resulting hyper-insulinemia affects ovarian follicular development and drives ovarian theca cells to produce excess androgen, causing hyperandrogenism, menstrual irregularities and polycystic ovaries.

The gut barrier-endotoxemia-inflammation mechanism or leaky gut as depicted in Fig. (2) is proposed as the explanation for chronic inflammation and IR [18]. Gut dysbiosis is thought to affect the intestinal epithelial barrier by modulating the immune system, which regulates the integrity of tight junction complexes through molecules such as zonulin [5]. Increased gut permeability leads to the translocation of Lipopolysaccharide (LPS) produced by intestinal flora into the circulation, causing endotoxemia [15, 18, 19]. Once LPS enters the circulation, LPS Binding Protein (LBP) binds with CD14 toll-like receptors of innate immune cells, causing immune system activation and insulin resistance. Further, LPS-induced macrophage activation expresses TNF and IL-6, which are related to IR.

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