Women's Therapeutics in the 21st Century

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A Holistic Approach

Edited by

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and Bimal Krishna Banik

Cambridge
Scholars
Publishing

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This book first published 2025

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-1-0364-5724-2
ISBN (Ebook): 978-1-0364-5725-9

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PREFACE

Women's health has long been a cornerstone of medical science, yet it remains a field with substantial unmet needs and evolving challenges. As we step into the 21st century, the landscape of women's therapeutics is witnessing transformative advancements, powered by cutting-edge research, precision medicine, and holistic approaches to care. This book, titled *Women's Therapeutics in the 21st Century: A Holistic Approach*, aims to serve as a comprehensive guide for healthcare professionals, researchers, and students, shedding light on the most pressing issues and innovations in women's health.

The chapters in this book are meticulously curated to address a wide array of conditions that significantly impact women's health. Beginning with **Chapter 1**, delve into the complexities of polycystic ovarian syndrome (PCOS), a multifaceted endocrine disorder that affects millions of women globally. This chapter provides a detailed overview of its pathophysiology, clinical manifestations, and emerging therapeutic strategies.

Chapter 2 explores recent advancements in the management of Endometriosis, a debilitating condition that often eludes timely diagnosis. The chapter highlights innovative medical, surgical, and integrative approaches that aim to improve patient outcomes.

Chapter 3 focuses on Uterine Leiomyomas, commonly known as fibroids, discussing their pathogenesis and the spectrum of therapeutic options ranging from pharmacological interventions to minimally invasive surgical techniques.

Cancer remains a critical area of concern in women's health. **Chapter 4** provides an in-depth analysis of cervical cancer, emphasizing recent advancements in treatment modalities, including immunotherapy and targeted therapies. This is followed by **Chapter 5**, which reviews the latest updates in ovarian cancer management and diagnostic advancements, and **Chapter 6**, represents a holistic perspective on uterine cancer treatment.

Chapter 7 shifts focus to vaginal cancer, providing insights into its diagnosis and therapeutic options, while **Chapter 8** discusses vulvar cancer, highlighting the importance of early detection and innovative treatments.

Chapter 9 extends this discussion to breast cancer, presenting current research trends and breakthroughs in its management.

Uterine serous carcinoma, an aggressive subtype of endometrial cancer, is examined in **Chapter 10**, offering readers a recent update on its clinical management. **Chapter 11** addresses sexually transmitted diseases (STDs), discussing the latest therapeutic perspectives and their implications for women's health.

Finally, **Chapter 12** explores the often-overlooked intersection of menopause and psychotic disorders, unveiling the untold stories of women navigating this complex phase of life. This chapter underscores the necessity of addressing mental health alongside physical health, advocating for a comprehensive approach to care.

This book is designed to be a valuable resource for a diverse audience, from clinicians and researchers to students and policymakers. By integrating traditional knowledge with modern scientific advancements, it aims to foster a deeper understanding of the challenges and opportunities in women's therapeutics.

We hope that this book not only informs but also inspires its readers to contribute to the advancement of women's health. As we continue to address the unique needs of women across the globe, let us strive to build a future where every woman has access to the care and support she deserves.

The authors aspire for this book to inspire students, researchers, and academic professionals to broaden their understanding and delve deeper into the field of women's health therapeutics while exploring innovative opportunities for research, education, and clinical advancements. Additionally, it aims to engage a wider audience, including healthcare policymakers and the general public, by presenting valuable insights into the evolving landscape of women's health in an accessible and impactful manner.

The completion of this comprehensive guide would not have been possible without the steadfast support of Cambridge Scholars Publishing. The authors extend their sincere gratitude to Alison Duffy, Commissioning Editor, and Sophie Edminson, Designer for their scientific acumen, constant encouragement, and invaluable guidance throughout this collaborative journey.

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ACKNOWLEDGEMENTS

We wish to express our sincere gratitude to all those who have contributed, directly or indirectly, to the successful completion of this work titled "Women's Therapeutics in 21st Century: A Holistic Approach". Our heartfelt thanks go to the all authors, whose dedication and insights into women health have provided valuable direction and inspiration for this study. Their commitment to advancing holistic and evidence-based therapeutic approaches continues to shape the future of women's healthcare.

We are deeply thankful to our mentors, colleagues and institutional authorities for their constant encouragement, constructive feedback, and academic support throughout this endeavor.

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Finally, we express our heartfelt gratitude to the Almighty, whose divine grace, blessings, and guidance have been our enduring source of strength and inspiration throughout this work.

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Chapter 1

Brief Insights into Polycystic Ovarian Syndrome

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1 Introduction

Polycystic Ovarian Disorder (PCOD) or Polycystic Ovary Syndrome, similarly recognized as Hyperandrogenic anovulation or Stein-Leventhal syndrome, is a common endocrinal disorder in women. It impacts about 6-15% of women of motherhood age globally. The major endocrine glands involved in the PCOS are the hypothalamus, pituitary gland, ovaries, adrenal gland and peripheral adipose tissues that together contribute to create a general imbalance [1].

Numerous tiny cysts, or sacs filled with fluid, developing in the ovaries but not releasing eggs consistently are referred to as polycystic ovarian disease. Hormone levels such as those of testosterone, progesterone, FSH, and LH are altered by the disruption of the ovulation process [2].

It is characterized by the presence of multiple cysts in the ovaries, hormonal imbalances, irregular or absent menstrual periods, and high levels of androgens (male hormones) in the body [3], representing a risk factor for further diseases such as cardiovascular disease and type 2 diabetes mellitus (DMT2) metabolic syndrome (MetS), recurrent miscarriage and depression and anxiety [4]. Polycystic ovarian disease (PCOD) was first described in 1935 by Irving F. Stein and Michael Leventhal [5].

Most symptoms of polycystic ovary syndrome (PCOS) usually occur during adolescence, when menstruation begins. However, some women may not experience symptoms till they are in their early to mid-20s. In individuals with PCOS, the ovaries contain more than ten follicles, which are detectable via ultrasound. Compared to a normal ovary, a polycystic ovary has a thicker layer, more follicles, and a denser central region. This centre is known as stroma which is where testosterone made. [6] It describes a condition where at least one ovary has an ovarian volume greater than 10 mL and at least one

ovary has an estimated ten small cysts, with diameters ranging from 2 to 9 mm, develop [7].

Generally, PCOS consist of the presence of any 3 criteria, oligo-anovulation, clinical or biochemical evidence of hyperandrogenism and the presence of polycystic ovaries on ultrasound examination. PCOS is medical condition in which there is an imbalance of female sex hormones, which includes increased levels of testosterone, DHEA-S, androstenedione, prolactin, and luteinizing hormone (LH), accompanied by estrogen levels that may be normal, elevated, or decreased. Hyperinsulinemia, insulin resistance and impaired glucose tolerance are very common in women with PCOS [8].

A systematic review utilizing the National Institutes of Health (NIH) diagnostic criteria estimates that 4–10% of women of reproductive age globally are likely to be affected by PCOS. According to data from the World Health Organization (WHO), 116 million women worldwide—or 3.4% of the total population—were diagnosed with PCOS in 2012. The syndrome's high incidence and associations with irregular menstruation, infertility, hair loss, and metabolic diseases highlight its substantial financial impact. Although most PCOS diagnoses happen between the ages of 20 and 30, the condition can appear at any age starting with the commencement of menstruation.

Approximately 1.55 million women of reproductive age suffer from this condition, which results in 0.43 million years of disability-adjusted life. Compared to 2007, the age-standardized incidence rate of PCOS among women of reproductive age increased by 1.45% to 82.44 per 100,000 in 2017. The most recent research indicates that PCOS is a chronic condition [9].

PCOS at Different Stages of Life

The progression of PCOS during different life stages is poorly known because of the paucity of cohort studies with long-term follow-up. One study analysed the biochemical and clinical traits of PCOS-afflicted women in comparison to wholesome controls, who first attended a medical centre an average around six years later, at the age of 29. This longitudinal study found a correlation between aging and an increased incidence of typical periods of menstruation, decreased amounts of androgen in the serum, and lower insulin resistance (IR) over time. However, the reasons behind the gradual decline of PCOS symptoms as women age remain unclear.

Additional studies have investigated PCOS features within specific age demographics, detailed as follows.

PCOS in childhood

The pathophysiology of PCOS seems to stem from a mix of genetic susceptibility and various environmental influences both before and after birth. Factors such as intrauterine growth restriction, being born small for gestational age, paired with elevated androgen levels during the prenatal period, may result in increased glucocorticoid production. This, in turn, could cause epigenetic changes that elevate the risk of developing PCOS.

PCOS in adolescence

PCOS is frequently identified during puberty, with common symptoms including menstrual irregularities, acne, and hirsutism. However, these signs often overlap with normal developmental changes during adolescence. Risk factors for developing PCOS contain a family past of the condition, being overweight or having a low birth weight, prenatal androgen exposure, precocious puberty, obesity, and insulin resistance. Diagnosing PCOS in adolescents requires more stringent criteria than in adults. It necessitates clear evidence of hyperandrogenism — like persistently high blood testosterone levels or moderate to severe hirsutism—along with evidence of ovulatory dysfunction persisting for over two years post-menarche.

Teenagers with PCOS should be encouraged to start living a healthy lifestyle right away because, according to recent studies, they are more likely to develop metabolic syndrome (MS). When a diagnosis of PCOS is made, considerations regarding IR symptoms and quality of life are essential. Adolescents may also be affected by obesity, being overweight, and hyperinsulinemia. Furthermore, eating conditions like bulimia, anorexia, and spree eating, as well as poor dietary habits featuring high-calorie, processed foods, are prevalent during adolescence. Thus, nutritional guidance, encouragement for Exercise and self-care ought to be comprise a comprehensive care strategy for teenage girls.

PCOS in women who have had menopause

Women who have a history of PCOS often continue to experience hyperandrogenism after menopause, along with ongoing metabolic abnormalities and an elevated risk of cardiovascular disease and metabolic

syndrome (MS). As a result, postmenopausal women who had PCOS during their reproductive years may still exhibit symptoms of the condition [10].

Symptoms of PCOS

Most of ladies are not even aware that they have PCOD. Early identification of PCOS is crucial, so it's important to be aware of its signs. While PCOS symptoms often emerge in early adulthood, they can also appear shortly after puberty. Anovulation leads to irregular or missed periods in many women with PCOS, though some may also develop ovarian cysts.

It presents with a variety of signs and symptoms:

- **Irregular periods:** Irregular or abnormal periods are the most common symptom of PCOD. Pay close attention for monthly cycle to help identify signs of PCOD.
- **Excessive facial and body hair (Hirsutism):** The growth of Excessive facial and body hair, known as hirsutism, is a mutual symptom of PCOD. Women with PCOD experience increased hair growth due to higher levels of androgens, the male hormones secreted by the ovaries. Hirsutism impacts around 70% of women with PCOS and serves as a common indicator of hyperandrogenism. This abnormal hair growth can manifest in various regions, including the face, arms, back, chest, thumbs, toes, and abdomen, and is associated with hormonal imbalances linked to PCOS.
- **Acne and Oily Skin:** Acne and oily skin are frequent problems resulting from hormonal disruptions in PCOD. The condition arises from an overproduction of male hormones, which can lead to severe cystic acne in some women. Acne is an inflammatory disorder that impacts the hair follicles as well as the sebaceous and apocrine glands associated with them. For a significant number of women dealing with acne, the main issue is the increased production of sebum, despite their serum androgen levels potentially being normal.
- **Mood Swings:** PCOD leads to hormonal imbalances and irregular periods, which can trigger sudden mood swings. As a result, depression and anxiety are common symptoms associated with the condition.
- **Weight gain:** Women with PCOD experience a surge in male hormones and insulin production, often resulting in unexpected weight gain. A typical indicator of PCOD is the buildup of fat in the lower belly area. The incidence of overheavy and overweightness amongst women with PCOS differs significantly by country. For instance, in Italy, 10% of women with PCOS are classified as overweight, whereas in Kuwait, this

percentage escalates to 37%. Research conducted in the US and Australia reveals that the mainstream of women with PCOS—between 61% and 76%—are classified as obese.

- **Heavy Bleeding:** Due to irregular periods, there is increased accumulation in the uterine wall, which leads to heavier bleeding during each menstrual cycle.
- **Hair Thinning:** Many women with PCOD experience hair loss, it can be severe or total. This is caused by hormonal imbalances in the body, with an excess of androgens leading to hair thinning or loss on the scalp.
- **Diabetes:** Generally speaking, women with PCOD have higher insulin levels, which makes them more vulnerable to diabetes. One of the main traits of PCOS is insulin resistance. An increased risk of type 2 diabetes, impaired glucose tolerance (IGT), and gestational diabetes mellitus (GDM) has been closely linked to PCOS, according to epidemiological study. Although there is still little data on its frequency, there is a strong correlation between PCOS and GDM; a recent meta-analysis found that women with PCOS are almost three times more likely to acquire GDM.
- **Pelvic Pain:** In addition to severe bleeding and headaches, women may experience pelvic discomfort during their menstrual cycles.
- **Sleep problems:** Many women with PCOS report difficulties with sleep, including insomnia. Sleep apnea, a condition often associated with PCOS, involves interruptions in breathing during the night, which affects sleep quality.
- **Skin Darkening:** Dark patches may appear on the skin of the body, including the neck, groyne, and beneath the breasts [11].

1.2 History

Women have suffered with PCOS for several centuries. However, the earliest report of problems related to the alterations in ovaries was reported in 1721; yet, only in the 1935 almost more than two decades later researchers shifted their focus towards this problem by officially acknowledging the occurrence of ovarian cysts.

The Development of PCOS as Distinct Syndrome: A Historical Perspective

Polycystic ovary syndrome (PCOS), first characterized by Stein and Leventhal, earned its name due to its distinct ovarian morphology. The researchers documented seven women exhibiting similar symptoms, including menstrual irregularities, hirsutism, and enlarged ovaries featuring multiple minor cavities. They supposed that abnormal hormonal stimulation

led to the development of bilateral cystic ovaries, a theory subsequently validated by additional studies. Over time, medical therapies such as clomiphene and follicle-stimulating hormone emerged as favoured alternatives to surgical ovarian resection. Nonetheless, interest in surgical options revived with the advent of laparoscopic techniques.

The introduction of ultrasound imaging for the ovaries marked a significant advancement, facilitating easier diagnosis of PCOS. However, this also resulted in the unintended identification of numerous women with polycystic ovaries but without other PCOS symptoms, leading to the use of the term "polycystic ovarian morphology," the implications of which continue to be debated. Critics argue that the extensive adoption of the Rotterdam criteria, which encompasses women with polycystic ovarian geomorphology lacking clinical or biochemicals signs of hyperandrogenism, may result in superfluous diagnoses and evaluations with potentially lifelong repercussions.

Despite extensive research, the precise cause of PCOS is not fully understood, and it is now familiar as a multifactorial disorder with a significant genetic influence. Although insulin resistance (IR) is frequently observed in women with PCOS, it is notably absent from the established diagnostic criteria. [12]

1.3 Epidemiology and Prevalence

A significant public health issue, polycystic ovarian syndrome (PCOS) is one of the most common hormonal conditions affecting women who are of reproductive age. According to estimates, the illness affects 8–13% of women in this group, and up to 70% of cases remain misdiagnosed.

The occurrence of PCOS is elevated amongst specific ethnic groups, which often practice more problems, particularly those linked to metabolic issues.

The biological and psychological effects of PCOS, particularly those related to obesity, body image and infertility, can lead to mental health challenges and social stigma [13].

Epidemiology of PCOS in India

The majority of the research that have looked into the prevalence of PCOS in India have used convenience sampling, which may not give a reliable picture of the condition's true prevalence in the population. In Tamil Nadu,

a pilot cross-sectional study found that 18% of young adolescent girls had PCOS. It was also shown that the percentage of PCOS cases among urban women was higher than that of their rural counterparts. Similarly, an urban community-based study in Mumbai found that the prevalence of PCOS was 10.7% based on the Androgen Excess Society criteria and 22.5% based on the Rotterdam criteria.

Based on NIH criteria, a study conducted in Lucknow on college-aged women (18–25 years old) with hirsutism and irregular menstruation revealed a low prevalence of PCOS of 3.7%. Additionally, 9.13% of young women attending a residential college in Andhra Pradesh met the Rotterdam criteria for PCOS, according to a study done there. According to research conducted in Chennai by Vidya Bharathi et al., 6% of women living in the community, both in rural and urban areas, had a PCOS diagnosis based on the Rotterdam criteria. According to international research, PCOS affects 4–10% of women who are of reproductive age. The variation in incidence based on different diagnostic criteria could account for the discrepancies observed in Indian studies. Hence, from the limited data available, it can be concluded that the prevalence of PCOS in India ranges from 3.7% to 22.5% [14].

According to estimates based on the NIH/NICHD criteria, between 4% and 8% of women who are of reproductive age have PCOS. Recent studies have consistently demonstrated that prevalence rates using the Rotterdam criteria are two to three times greater than those generated from the NIH/NICHD criteria, highlighting the possibility that the prevalence of PCOS may vary depending on the diagnostic criteria used.

Type 1, Type 2, and gestational diabetes are all linked to a higher incidence of PCOS. In research conducted by Escobar-Morreale et al., 85 Caucasian women with type 1 diabetes mellitus were evaluated for PCOS according to NIH/NICHD standards, revealing that 16 women (18.8%) were diagnosed with the disorder. Following this, Codner et al. examined 42 women with type 1 diabetes alongside 38 age- and BMI-matched controls using ESHRE/ASRM criteria, discovering a prevalence of 40.5% in the type 1 diabetes group compared to just 2.6% in the control group.

This resulted in a relative risk of 15.4 (95% confidence interval [CI] 2.2–110.2; $P<0.0001$) for developing polycystic ovary syndrome (PCOS) among those with type 1 diabetes. For individuals with type 2 diabetes, the incidence of polycystic ovaries (PCO) is particularly high, with 82% of women affected. Based on the NIH/NICHD criteria, the estimated

prevalence of PCOS among women with type 2 diabetes is 26.7%. Additionally, research on gestational diabetes revealed that 15 out of 94 women (16%) with the condition were diagnosed with PCOS, whereas only six out of 94 women (6.4%) without gestational diabetes were diagnosed (P=0.03).

Women with epilepsy have also shown a heightened occurrence of reproductive disorders, including PCOS. Using NIH diagnostic criteria, Bilo et al. identified PCOS in 13 out of 50 women (26%) with epilepsy. Moreover, the prevalence of PCOS is linked to various medical conditions. Typically, weight gain precedes the clinical symptoms of PCOS, and adopting a healthier lifestyle has been proven beneficial in shedding excess weight, reducing abdominal fat, lowering testosterone levels, easing insulin resistance, and lessening hirsutism among women with PCOS. In a cohort of women seeking weight loss support, a prevalence rate of 28.3% for PCOS was found. However, in an unselected general population, the prevalence of PCOS showed no significant differences across various obesity categories. Rates of PCOS prevalence in underweight, normal-weight, overweight, mildly obese, moderately obese, and severely obese women were recorded at 8.2%, 9.8%, 9.9%, 5.2%, 12.4%, and 11.5%, respectively. The authors concluded that while obesity may increase the risk of developing PCOS, its effect is relatively modest.

A familial history of PCOS is recognized as a risk factor for the condition. The clustering of cases within families has led to PCOS being classified as a heritable disorder. A high prevalence of PCOS or its features among first-degree relatives suggests a genetic influence. A genome-wide association study conducted in Han Chinese populations identified susceptibility loci on chromosomes 2p16.3, 2p21, and 9q33.3. Several of these findings were replicated in European cohorts, particularly concerning the THADA locus on chromosome 2p21 and the DENND1A locus on chromosome 9p33.3. These shared genetic susceptibility markers suggest that PCOS is an ancient disorder likely to have originated before human migration from Africa. [15]

2 Pathophysiology

2.1 Genetics in PCOS

The evidence that PCOS may be genetically determined initially came from twin studies, where the incidence of PCOS was twice as high in women with an affected twin as compared to the rest of population. Candidate gene approach worldwide has identified many susceptibility genes including

cytochrome P1A1 (*CYP1A1*), *CYP11A, CYP17A1, CYP19*, 17β-hydroxysteroid dehydrogenase (*HSD17B6*), androgen receptor (*AR*), sex hormone-binding globulin (*SHBG*), insulin receptor (*INSR*), insulin receptor substrate 1 (*IRS1*), peroxisome proliferator-activated receptor gamma (*PPAR-γ*), follicle stimulating hormone receptor (*FSHR*), luteinizing hormone/chorionic gonadotropin receptor (*LHCGR*), anti-Mullerian hormone receptor type 2 (*AMHR2*), interleukin (*IL*) IL-1A, IL-1B and IL-6, whereas genome-wide association studies have identified many susceptibility loci including THADA, DENND1A, LHCGR, FSHR, C9orf3, YAP1, GATA4,-NEIL2 and ERBB4. [16]

Genes involved in ovarian and adrenal steroidogenesis:

a. Cytochrome P450 (CYP11α): This gene encoded for cleaving of cholesterol side chains. The polymorphism region of the CYP11α promoter region comprises (tttta)n, a pentanucleotide that initiates at the ATG transition site. Variable number tandem repeats or VNTRs, are important for the expression of CYP11α, which are mutated in PCOS women (the four repeat unit allele is lacking). This summarizes the relationship between PCOS and (tttta)n polymorphisms. However, more recent research was unable to validate the hypothesis that (tttta)n polymorphisms and PCOS are related.

b. Cytochrome P450 21-hydroxylase (CYP21): The CYP21 gene encodes an enzyme 21 hydroxylase that is necessary for the body to synthesize the two essential hormones cortisol and aldosterone. Congenital adrenal hyperplasia (CAH), a disorder marked by excessive hormone levels that might affect reproductive health, can result from mutations in the CYP21 gene. Mutation at P30L, V281L, and P453S have high risk of developing PCOS.

c. Cytochrome P450c17a (CYP17): CYP17 encodes for 17-alpha hydroxylase and 17/20-lyase enzymes, which catalyse the adaptation of pregnenolone to 17-hydroxypregnenolone and progesterone to 17-hydroxyprogesterone (Khan et al., 2003). In contrast, women with PCOS show an increased blood level of 17-alpha hydroxylase in response to GnRH agonists. Recent studies have revealed that serine phosphorylation plays a role in androgen production by regulating the post-translational control of 17, 20-lyase activity. However, it remains unclear which serine residues are phosphorylated and which kinase is responsible for triggering the phosphorylation. Research on the Chilean population found that polymorphism C > T in CYP17 is linked to PCOS advancement. A polymorph in the promoter region linked to PCOS was discovered.

d. Cytochrome P450arom (CYP19) or aromatase: CYP19 synthesis C18 from C19 steroids i.e., estrogens from androgens. CYP19 may function as a genetic modulator of the hyperandrogenic phenotype of PCOS even if it may not be a key genetic driver of PCOS. Short CYP19(TTTA)n alleles (nine to few repeats) may have a role in prenatal androgenization development of the PCOS phenotype in adults. [17]

2.2. Genes Involved in Steroid Hormone Effects

Androgen receptor (AR):

The ovaries and other androgen-responsive tissues throughout the body depend on this for growth and proper operation. Androgens are male sex hormones that are also present in females, albeit in less amounts, and are crucial for regulating ovarian function. The ARgene comprises CAG polymorphism repeats ranging from 11 to 31; the most frequent variant has 20 repeats. The AR transcriptional activity is inversely proportional to the extent of the polymorphic repeats. Changes in the androgen receptor gene might cause the ovaries to become more sensitive to androgens, which would interfere with regular ovarian function. This may exacerbate the symptoms of PCOS that are typical to the condition, including ovarian cysts, irregular menstruation periods, hirsutism, or excessive hair growth.

Sex Hormone-Binding Globulin Gene (SHBG):

Synthesis of a protein that contains 373 amino acids. These proteins are responsible for controlling sex hormones. Lowering of SHBG due to mutation at VNTR of $(TAAAA)_n$ of polymorphic regions leads to PCOS. VNTR repeats should be less than 8 repeats.

Genes involved in gonadotropin action and regulation:

The LH gene codes for the luteinizing hormone production. PCOS may result from excessive production and dysfunction of LH. The reduction of FSH (follicle stimulating hormone), which is essential for adaptation of androgen to estrogen, is the result of the negative feedback reaction in the increase of LH. The reason for the surge is a point mutation in the β-subunit of LH at positions 8 and 15. At position 8, arginine (CGG) replaces tryptophan (TGG), while at position 15, threonine (ACC) replaces isoleucine (ATC). Another variation of LH includes serine at amino-acid 102 instead of glycine. Menstrual diseases are significantly influenced by variations in LH.

Genes involved in insulin action and secretion:

The insulin gene is not directly involved in the development of polycystic ovarian syndrome (PCOS). The insulin resistance and PCOS are clearly correlated. One sign of insulin resistance, a condition in which the body's cells become less sensitive to the effects of insulin, is hyperinsulinemia, or elevated blood levels of insulin. This may affect the body in several ways, such as causing the ovaries to produce more androgen, interfering with normal ovarian function, and exacerbating the symptoms that are specific to PCOS. A unique genetic component at the 5' insulin gene called the class III allele has been linked to PCOS. This allele has polymorphisms with variable numbers of tandem repeats that control the expression of genes. In addition to impairing regular ovarian function, insulin resistance can also result in ovarian cyst development and anovulation, or the absence of ovulation. It is believed that the interaction between insulin and other hormones that regulates ovarian function, such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH), ultimately mediates these effects. Insulin receptor gene: Insulin receptor composed of 2 α and β subunits of heterotetrametric glycoprotein encoded by insulin receptor gene. Since the α and β subunits have 1370 amino acids, it was formerly thought the dysfunction of insulin receptors was the cause of insulin resistance, a feature of PCOS. Multiple studies were conducted to validate the correlation between IRS-1 and IRS-2 and PCOS, but no significant results were found. These genes are phosphorylated by the INS receptor's tyrosine kinase activity. In an attempt to determine a connection between PCOS and many polymorphisms, the purpose of the insulin receptor remained affected. The α-glucosidase inhibitors such as bioactive peptides, phytocompounds, and synthetic compounds could be the possible approach to reduce type 2 diabetes mellitus-linked PCOS. [18]

2.3 Insulin Resistence and Hyperinsulinemia

Insulin plays a crucial role in regulating both lipogenesis and glucose levels. Beyond its impact on starch, obese, and protein metabolism, insulin also functions as a mitogenic hormone. Its activities are facilitated by insulin receptors located in different tissues within the hypothalamic-pituitary-ovarian (HPO) axis. Insulin increases steroidogenesis by increasing the action of associated trophic hormones in organs that produce steroids, such as the adrenal cortex and ovaries. Hyperinsulinemia contributes significantly to the overproduction of androgens because insulin mimics the effects of LH and indirectly stimulates GnRH. Additionally, insulin lowers

sex hormone binding globulin (SHBG) levels, an essential protein that controls testosterone levels. Lower SHBG levels result in increased free androgens, contributing to PCOS symptoms like hirsutism, alopecia, and acne. Research indicates that alleviating insulin resistance can lower androgen levels and ameliorate the disease condition.

The progress of insulin struggle in PCOS is affected by a mix of non-genetic factors, both inside and outside the uterus, genetic predispositions, and altered reactions to excess energy. Various molecular mechanisms contribute to insulin resistance in PCOS, including high levels of free fatty acids, increased cytokine release, elevated testosterone, and compromised post-receptor insulin function. Insulin resistance (IR) is a metabolic disorder marked by decreased cellular response to insulin signals and is viewed as a primary influence in the emergence of metabolic issues in PCOS. Women with PCOS frequently suffer from insulin resistance and hyperinsulinemia, which can outcome in health problems such as type 2 diabetes and reduced glucose tolerance. Hyperinsulinemia, linked to insulin struggle, leads to hypertrophy of theca cells in the ovaries, which can cause anovulation and infertility. Furthermore, insulin enhances the activity of related trophic hormones to support steroidogenesis in steroid-producing tissues like the ovaries and adrenal cortex. Hyperinsulinemia is the chief reason of extreme androgen creation from the ovaries and adrenal glands, as it amplifies the effect of LH. It also diminishes the production of sex hormone binding globulin (SHBG), an important protein that regulates testosterone levels, leading to higher levels of free circulating testosterone [19].

2.4. Role of Lifestyle Factors

Etiological Role of Environmental Pollutants

Research indicates that environmental contaminants like heavy metals, insecticides, and endocrine-disrupting chemicals (EDCs) have a profound impact on human health and fertility. Increasing data suggests that these impurities donate to the onset of PCOS. Research revealed that women with PCOS who exhibit hyperandrogenism have elevated BPA serum levels compared to those without hyperandrogenism and healthy controls. Another investigation create a helpful link between increased BPA blood levels and testosterone serum levels in women with PCOS versus healthy women. In case-control research, examined the association between environmental contaminants and PCOS and found that women with PCOS had higher serum levels of perfluorooctanoate and perfluorooctane sulfonate. Additionally, phthalate exposure and PCOS were found to be negatively

correlated in this study. Women with PCOS had lower urine levels of monobenzyl phthalate (mBzP), which may indicate problems with xenobiotic metabolism. At first, it was believed that EDCs like BPA and phthalates mostly impacted the nuclear hormone system's thyroid, estrogen, progesterone, and androgen receptors. However, later studies have shown that EDCs can directly impact steroidogenesis and hormone metabolism, as well as non-nuclear hormone receptors, orphan receptors, and neurotransmitter receptors. EDCs are ubiquitous contaminants that have been extensively studied as potential environmental causes of Exposure to certain EDCs during developmental stages might permanently change metabolic, reproductive, and neuroendocrine functions, possibly raising the risk of PCOS in individuals with genetic predispositions or hastening the syndrome progression over time. EDCs might also induce epigenetic modifications in the DNA of the female reproductive system, potentially impacting future generations and passing on traits associated with PCOS. In summary, EDCs may contribute to the development of PCOS by interfering with the control of local paracrine and autocrine systems, as well as hypothalamic-gonadal hormones.

A variety of research has established a direct link between the occurrence of PCOS, smoking, and being exposed to cigarette smoke. Research that included women with PCOS who have oligo-anovulation, those with normal ovulation in PCOS, and a control group of well women displayed that smoking was related with ovulatory dysfunction, and this relationship was influenced by the amount of smoking. Smoking triggers an inflammatory reaction, which includes an rise in mononuclear cells, mitochondrial issues, a drop in glutathione (GSH) levels, reduced oxygen consumption, and an oxidative environment characterized by decreased antioxidant levels, all of which are frequently observed in PCOS. These inflammatory responses have the potential to affect enzymes and disrupt theca cell steroidogenesis. Cigarette smoke, coal, gas, wood, trash, and high-temperature cooked meat all include polycyclic aromatic hydrocarbons (PAHs), which contribute significantly to air pollution and are linked to an increased risk of PCOS. In women exposed to air pollutants such nitrogen oxides, sulfur dioxide, PAHs, and fine particulate matter (PM 2.5), inflammatory markers may rise. This could disrupt normal steroidogenesis and contribute to the development of PCOS. Exposure to fine particle air pollutants and gases, such as SO2, NO, NO2, NOx, and PM2.5, was linked to an increased incidence of PCOS, according to a population-based study conducted in Taiwan. Additionally, animal models bolster according to recent research, the direct exposure of pregnant rats to either fungicide vinclozolin or insecticide DDT was associated with the

development of ovarian abnormalities consistent with PCOS in three subsequent generations via epigenetic processes [20].

Physical and Emotional Stress

Despite the scarcity of data on how stress influences PCOS, it is widely recognized that PCOS adversely impacts self-esteem and psychological well-being. Prolonged stress results in the enlargement and proliferation of fat cells, a consequence of glucocorticoids' effect on the development of pre-fat cells. This stress is also associated with the announcement of adipokines and the recruitment and stimulation of immune cells in fat tissue. Moreover, ongoing stress exacerbates inflammation by increasing the absorption of inflammatory markers such as IL-6 and TNF-α, and it upsets the equilibrium between oxidative and antioxidative processes. Additionally, chronic stress significantly contributes to insulin resistance (IR).

The hypothalamic-pituitary-adrenal (HPA) axis is activated by stress, which causes cortisol to be secreted. Cortisol fosters IR by promoting the buildup of abdominal fat, enhancing glucose production from non-carbohydrate sources, and increasing fat breakdown, as well as boosting liver glucose output. Stress also plays a role in raising insulin concentrations. Other possible impacts of stress on PCOS involve disrupting anti-Müllerian hormone (AMH) function and changing sex hormone levels [21].

3. Diagnosis

3.1 Diagnostic Criteria (Rotterdam, NIH, AE-PCOS)

Diagnostic Criteria for PCOS

The diagnosis of Polycystic Ovary Syndrome (PCOS) relies on particular medical, hormonal, and imaging results. Three primary diagnostic standards are commonly utilized: the Rotterdam Norms, the NIH Criteria, and the AE-PCOS Society Norms.

1. Rotterdam Criteria (2003)

The PCOS Consensus Workshop Group, supported by ESHRE/ASRM, developed the Rotterdam criteria. Two of the three characteristics listed below must be present for a diagnosis to be made:

- *Oligo-ovulation or Anovulation:*

  Irregular menstrual cycles (cycle length >35 days or <8 cycles/year).

- Clinical or Biochemical Hyperandrogenism:

Medical signs: hirsutism (Ferriman-Gallwey score >8), acne, androgenic alopecia.

Biochemical: Elevated serum androgens (e.g., testosterone).

- *Polycystic Ovarian Morphology on Ultrasound:*

  Occurrence of ≥12 follicles (2-9 mm in distance) per ovary and/or ovarian volume >10 cm^3.

This broader definition includes heterogeneous phenotypes but has been criticized for potentially over diagnosing PCOS, especially in adolescents.

2. NIH Criteria (1990)

The National Institutes of Health (NIH) criteria are stricter and need both of the following for diagnosis:

- Hyperandrogenism (clinical and/or biochemical).
- Chronic Anovulation (irregular or absent ovulation).

Polycystic ovarian morphology is not mandatory under the NIH criteria. This definition focuses on the classic phenotype of PCOS and excludes milder cases, making it more specific but less inclusive.

3. AE-PCOS Society Criteria (2006)

The significance of hyperandrogenism is emphasized by the Androgen Excess and PCOS Society criteria.

Diagnosis necessitates:

- Hyperandrogenism (clinical and/or biochemical):

  This is a mandatory criterion.

- Ovarian Dysfunction:

  Oligo-anovulation or polycystic ovarian morphology.

The AE-PCOS norms exclude other causes of androgen excess (e.g., Cushing's syndrome, androgen-secreting tumours), thereby targeting PCOS cases with clear androgen excess.

Clinical Relevance

The Rotterdam norms are the record broadly used due to their inclusiveness, whereas the NIH norms are stricter and focus on the classical form of PCOS. The AE-PCOS Society criteria prioritize hyperandrogenism as the defining feature of the syndrome.

Proper diagnosis is critical to ensure appropriate management and to differentiate PCOS from other conditions like thyroid disorders, hyperprolactinemia, and androgen-secreting tumours. [22]

3.2 Laboratory Investigations

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder affecting reproductive-aged women. The role of lab tests is crucial in both diagnosing and managing PCOS due to the variability in how it presents clinically. The diagnosis is based on the Rotterdam norms, which necessitates the occurrence of at least two out of three conditions: symbols of high androgen levels, irregular ovulation, and the occurrence of polycystic ovaries identified by ultrasonography.

Key laboratory tests include hormonal assays to evaluate hyperandrogenism. Elevated total testosterone and free androgen index (FAI) are hallmark findings, while dehydroepiandrosterone sulphate (DHEAS) may also be elevated. To law out other sources of hyperandrogenism, 17-hydroxyprogesterone helps exclude congenital adrenal hyperplasia. Thyroid dysfunction and hyperprolactinemia are assessed using thyroid-stimulating hormone (TSH) and prolactin levels, respectively.

Although not diagnostic, gonadotropin levels, specifically the ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH), are frequently increased (>2:1) in PCOS. Since insulin resistance is a prevalent symptom, metabolic evaluations such as fasting blood glucose, insulin levels, and Homeostatic Model Assessment for Insulin Resistance (HOMA-

IR) are crucial. To detect dyslipidaemia and impaired glucose metabolism, a lipid profile and glucose tolerance test (OGTT) are advised.

Further, transvaginal ultrasound detects polycystic ovarian morphology (≥20 follicles or ovarian volume ≥10 ml). These laboratory and imaging studies aid in differentiating PCOS from other disorders like Cushing's syndrome or hypothyroidism.

Comprehensive evaluation of hormonal, metabolic, and imaging findings ensures an accurate diagnosis and effective management strategy for PCOS. [23]

3.3 Imaging Studies

Imaging studies play a pivotal role in diagnosing Polycystic Ovary Syndrome (PCOS) by assessing ovarian morphology and excluding other gynaecological conditions. The primary imaging modality is transvaginal ultrasound (TVUS), which provides detailed visualization of the ovaries.

In PCOS, ultrasound typically reveals polycystic ovarian morphology (PCOM), characterized by the occurrence of ≥20 follicles (2–9 mm in diameter) per ovary and/or improved ovarian volume ≥10 mL, as per the 2018 International PCOS Guidelines. These findings reflect disrupted folliculogenesis and an excess of minor antral cavities. The “string of pearls” appearance, where cystic follicles line the periphery of the ovary, is another classic but not mandatory feature of PCOM.

3D ultrasound further enhances follicle count accuracy and ovarian volume measurement, improving diagnostic precision. Additionally, Doppler ultrasound evaluates ovarian stromal blood flow, often showing increased vascularization in PCOS due to hyperandrogenism and stromal hypertrophy.

In cases where ultrasound findings are inconclusive or transvaginal access is not feasible (e.g., in virginal patients), transabdominal ultrasound may be performed, though it is less sensitive. Magnetic Resonance Imaging (MRI) can provide an alternative modality, offering superior soft-tissue contrast and clearer imaging of the ovaries, but it is hardly needed for repetitive diagnosis.

Imaging studies complement laboratory findings to confirm PCOS and exclude other ovarian pathologies such as tumour’s or cysts, ensuring accurate diagnosis and management [24].

4. Complications and Comorbidities of PCOS

4.1 Infertility and Reproductive Challenges

Polycystic Ovary Syndrome (PCOS) ranks as a important reason of infertility, impacting as many as 70-80% of women diagnosed with it. The primary factor contributing to infertility in PCOS is ovulatory dysfunction characterized by oligo-ovulation (infrequent ovulation) or anovulation (nonappearance of ovulation). This results from hormonal imbalances, particularly elevated androgens (hyperandrogenism) and impaired regulation of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). High LH levels and insulin struggle lead to excessive androgen production, which avoids the growth of a dominant follicle, thereby hindering ovulation.

Additionally, insulin resistance—a hallmark of PCOS—causes hyperinsulinemia, which additional stimulates ovarian theca cells to produce androgens. Elevated insulin too suppresses hepatic creation of sex hormone-binding globulin (SHBG), increasing free androgens in circulation and exacerbating reproductive dysfunction. These hormonal disruptions manifest clinically as irregular menstrual cycles, polycystic ovaries, and subfertility.

Womens thru PCOS also face advanced hazards of recurrent pregnancy loss, gestational diabetes mellitus (GDM), preeclampsia, and preterm delivery, posing challenges even after conception. Furthermore, obesity, often coexisting with PCOS, worsens insulin resistance and contributes to poor fertility outcomes.

Treatment strategies for infertility in PCOS include:

- ✓ Lifestyle changes: Diet, exercise, and weight loss to increase insulin sensitivity and induce ovulation again.
- ✓ Ovulation induction drugs: First-line agents include clomiphene citrate and letrozole.
- ✓ Insulin sensitizers: Metformin helps reduce insulin resistance and improve ovulatory function.
- ✓ Advanced therapies: In resistant cases, gonadotropins, ovarian drilling, or assisted reproductive technologies (ART) such as in-vitro fertilization (IVF) are considered.

The evidence provided is based on widely accepted clinical guidelines, peer-reviewed research, and authoritative reviews on PCOS. The following references are commonly cited sources for this data: [25]

4.2 Risk of Type 2 Diabetes Mellitus

Women with Polycystic Ovary Syndrome (PCOS) are at a significantly higher risk of developing Type 2 Diabetes Mellitus (T2DM) due to insulin resistance (IR) and hyperinsulinemia, which are hallmark features of the syndrome. Insulin struggle disturbs up to 70-80% of women with PCOS, particularly those who are obese, but it can also occur in lean individuals.

Pathophysiology:

In PCOS, insulin resistance reduces glucose acceptance in peripheral tissues, ensuing in hyperglycemia and compensatory hyperinsulinemia. Excess insulin stimulates ovarian theca cells to produce more androgens, exacerbating hyperandrogenemia and further disrupting the metabolic and reproductive systems. Over time, this metabolic dysfunction increases the likelihood of progressing to reduced glucose tolerance (IGT) and T2DM.

Prevalence:

Studies indicate that women with PCOS have a **4-10 times higher hazard** of evolving T2DM related to the general population. A significant proportion of women develop glucose abnormalities before the age of 40. For instance, up to **40%** of women with PCOS exhibit IGT or diabetes by their fourth decade.

Screening and Prevention:

Early detection through **Oral Glucose Tolerance Testing (OGTT)** is recommended for all women thru PCOS, particularly those thru obesity, Diabetes in the family or a history of gestational diabetes. Weight loss, dietary adjustments, and increased physical activity are examples of lifestyle changes that can dramatically enhance insulin sensitivity and lower the risk of diabetes. Pharmacological interventions like **metformin** can also be beneficial in managing IR and preventing progression to T2DM. [26]