Review Article

Polycystic Ovary Syndrome Phenotypes: Beyond Rotterdam Toward an Integrated Clinical, Metabolic, and Biological Classification

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Abstract

Polycystic ovary syndrome is a heterogeneous disorder whose diagnostic and phenotypic understanding has evolved considerably over time. Early definitions focused mainly on menstrual irregularity, hyperandrogenism, and polycystic ovaries, with emphasis placed on reproductive manifestations rather than metabolic consequences. The National Institutes of Health criteria later prioritized hyperandrogenism and chronic anovulation, offering a clearer but narrower diagnostic structure. The Rotterdam criteria subsequently broadened the definition by incorporating hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, thereby recognizing

wider phenotypic diversity, although also introducing controversy regarding overdiagnosis and limited prognostic precision. Among the classical phenotypes, Phenotypes A and B are generally associated with the greatest metabolic burden, including higher insulin resistance, dyslipidemia, and cardiometabolic risk, whereas Phenotype C tends to preserve ovulation and Phenotype D remains the mildest and most debated form. However, the Rotterdam model is limited by marked heterogeneity within each phenotype, poor ability to predict long-term metabolic and reproductive outcomes, and insufficient representation of the syndrome as a dynamic systemic disorder. Current evidence suggests that phenotypic diversity is shaped by insulin resistance, ovarian androgen excess, neuroendocrine dysregulation, adipose tissue dysfunction, inflammation, oxidative stress, and genetic and epigenetic influences. As a result, emerging models now classify polycystic ovary syndrome according to metabolic, reproductive, hyperandrogenic, morphologic, psychosocial, and cluster-based patterns. These approaches support more accurate risk stratification, more individualized treatment, and a transition toward precision medicine, although their implementation remains limited by lack of consensus, variable access to biomarkers, and difficulty integrating complex subclassifications into routine clinical practice.

Key words

Polycystic ovary syndrome, Phenotypes, Hyperandrogenism, Insulin resistance, Rotterdam criteria, Precision medicine.

Introduction

Phenotypic classification is important in polycystic ovary syndrome because the disorder manifests through diverse clinical presentations, with each phenotype showing distinct clinical and biochemical features. The four primary phenotypes include different combinations of ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology (PCOM). In this context, phenotype-based stratification contributes directly to clinical management, since it helps tailor treatment plans according to the characteristics of each presentation. For example, women with hyperandrogenism and ovulatory dysfunction have a higher risk of metabolic complications and may therefore require more intensive management [1, 2]. In addition, phenotypic classification has important prognostic implications, as different phenotypes are associated with varying risks of metabolic syndrome, cardiovascular disease, and infertility, all of which influence long-term health outcomes [3].

Although the Rotterdam criteria remain widely used, they do not fully capture the heterogeneity of polycystic ovary syndrome. These criteria focus on three main features, namely hyperandrogenism, ovulatory dysfunction, and PCOM, but they do not adequately address metabolic and psychological aspects of the disorder [4, 5]. As a result, broader approaches have been increasingly proposed in recent studies. These integrative frameworks seek to incorporate genetic, metabolic, and environmental factors, with the aim of achieving more precise phenotypic classifications and, consequently, more personalized treatment strategies [6, 7].

Within this evolving perspective, emerging phenotypic approaches have begun to expand the understanding of the syndrome beyond traditional definitions. Data-driven subtypes identified through unsupervised clustering have revealed new forms of polycystic ovary syndrome based on clinical variables, such as hyperandrogenic polycystic ovary syndrome and polycystic ovary syndrome associated with obesity, each of which appears to follow distinct reproductive and metabolic trajectories [6]. At the same time, advances in genomics and biomarker research are paving the way for more

accurate phenotypic differentiation. In particular, Anti-Müllerian hormone (AMH) and other hormonal markers are being explored as potential diagnostic tools that may refine classification and improve the identification of clinically meaningful subgroups [2, 7].

The objective of this article is to analyze the phenotypes of polycystic ovary syndrome beyond the Rotterdam criteria, with emphasis on their clinical, metabolic, hormonal, and biological heterogeneity, as well as on emerging phenotypic classification approaches that may improve diagnostic precision, prognostic stratification, and individualized clinical management.

Methodology

This manuscript was developed as a structured narrative review aimed at providing an updated and clinically integrated analysis of polycystic ovary syndrome phenotypes beyond the Rotterdam criteria, with particular emphasis on phenotypic heterogeneity, pathophysiological diversity, limitations of conventional classification systems, and emerging models of clinical and biological stratification. The review was conducted in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) framework and followed a predefined methodological protocol established prior to literature screening. Given the marked variability in reproductive, endocrine, metabolic, and psychological manifestations of polycystic ovary syndrome, a narrative interpretative synthesis was selected over quantitative pooling in order to integrate diagnostic, mechanistic, and prognostic dimensions into a coherent and clinically applicable framework. Special attention was given to the classical Rotterdam phenotypes, the controversy surrounding non-hyperandrogenic presentations, the metabolic and reproductive implications of different phenotypic patterns, and the potential role of biomarkers, clustering approaches, and precision medicine models in refining classification. The objective was to provide a structured synthesis capable of supporting a more individualized and biologically informed understanding of polycystic ovary syndrome in contemporary clinical practice.

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, including peer-reviewed articles published in English or Spanish between January 2020 and December 2025. The final search was performed in March 2026. This timeframe was selected to capture contemporary advances in diagnostic criteria, phenotypic stratification, endocrine and metabolic profiling, biomarker development, and emerging approaches to subclassification in polycystic ovary syndrome. Foundational studies were incorporated when necessary to contextualize the historical evolution of diagnostic frameworks and the biological basis of phenotypic diversity. The search strategy combined MeSH and free-text terms using Boolean operators related to polycystic ovary syndrome, PCOS phenotypes, Rotterdam criteria, hyperandrogenism, ovulatory dysfunction, polycystic ovarian morphology, insulin resistance, metabolic phenotype, reproductive phenotype, Anti-Müllerian hormone, biomarkers, cluster analysis, and precision medicine. Searches were conducted in titles and abstracts as well as indexed subject headings to maximize sensitivity.

The initial search yielded 160 records. After removal of duplicates, 118 articles remained for title and abstract screening. Of these, 75 underwent full-text evaluation, and 26 studies were included in the final synthesis. Selection was performed independently by two authors, with disagreements resolved through discussion and consensus. Exclusion criteria comprised non-peer-reviewed publications, isolated case reports, editorials without substantive clinical or phenotypic analysis, redundant datasets, studies focused exclusively on treatment efficacy without phenotype-specific interpretation, and articles not directly addressing classification, pathophysiological heterogeneity, clinical

implications, or emerging subclassification models in polycystic ovary syndrome.

Eligible studies included observational cohorts, case-control studies, systematic reviews, meta-analyses, expert consensus statements, and contemporary international guidelines from reproductive endocrinology, gynecology, metabolism, and women's health societies. Priority was assigned to multicenter investigations, studies using clearly defined diagnostic criteria, and research evaluating endocrine, metabolic, reproductive, psychological, and biomarker-based distinctions among phenotypic groups. Extracted variables included study design, diagnostic criteria applied, phenotype classification, degree of hyperandrogenism, ovulatory status, presence of polycystic ovarian morphology, metabolic parameters, reproductive outcomes, psychological correlates, and proposed biomarkers or subclassification models. Methodological quality and internal validity were assessed narratively, considering risk of bias, sample size, diagnostic consistency, population characteristics, reproducibility of phenotype definitions, and coherence of reported clinical outcomes. In cases of conflicting evidence, greater interpretative weight was assigned to higher-level evidence and guideline-supported recommendations.

Reference lists of included studies were manually screened to identify additional relevant publications. Given its narrative design, this review is subject to potential selection bias and does not provide pooled quantitative estimates. Artificial intelligence–based tools were used exclusively to assist in literature organization and structural coherence, whereas critical appraisal, synthesis, and final interpretation were conducted independently by the authors to preserve methodological rigor.

Evolution of the Diagnostic and Phenotypic Concept of Polycystic Ovary Syndrome

Historically, polycystic ovary syndrome was identified through manifestations such as menstrual irregularity, hyperandrogenism, and polycystic ovaries, with the primary focus placed on reproductive health [8]. As a result, the initial tendency was to regard polycystic ovary syndrome mainly as a gynecologic disorder, which led to its metabolic implications being overlooked [1]. Subsequently, the National Institutes of Health criteria emphasized hyperandrogenism and chronic anovulation, thereby excluding milder or non-classical presentations [2]. This framework offered the strength of providing a clear diagnostic structure centered on the most severe manifestations. However, it also had important limitations, since it excluded many women with milder symptoms and may therefore have underestimated the true prevalence of the syndrome [5].

Later, the Rotterdam criteria, introduced in 2003, expanded the diagnostic framework by including hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, requiring the presence of two out of these three criteria for diagnosis [9]. This broader approach made it possible to identify a greater number of phenotypic categories and, in doing so, acknowledged the heterogeneity of the syndrome [1]. Nevertheless, these criteria have also been criticized for the possibility of overdiagnosing polycystic ovary syndrome by including women with milder symptoms [5]. In contrast, the perspective of the Androgen Excess and Polycystic Ovary Syndrome Society placed greater emphasis on androgen excess as a central feature of polycystic ovary syndrome, which sparked debate regarding the validity of non-hyperandrogenic phenotypes [2]. This view contributed substantially to the phenotypic discussion by underscoring the importance of androgen excess in understanding the syndrome [9].

These evolving definitions have had a direct impact on phenotypic classification, since the prevalence of polycystic ovary syndrome varies significantly depending on the diagnostic criteria applied, leading to diagnostic inconsistency across populations and studies. In turn, these differences influence both research interpretation and clinical management, because the use of different criteria may result in different treatment approaches and health outcomes [10].

Classical Rotterdam Phenotypes

Phenotype A, defined by the coexistence of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, is generally considered the most severe form of polycystic ovary syndrome. This phenotype is characterized by a marked endocrine and metabolic burden and is commonly associated with significant disturbances such as insulin resistance and dyslipidemia [2, 11]. In addition, women with this phenotype frequently present with higher body mass index, greater waist circumference, and more pronounced insulin resistance, all of which contribute to an increased risk of type 2 diabetes mellitus and cardiovascular disease [12].

Phenotype B, which includes hyperandrogenism and ovulatory dysfunction in the absence of polycystic ovarian morphology, shares many similarities with Phenotype A in terms of reproductive and androgenic burden. Despite lacking the morphological ovarian component, it is often associated with severe metabolic dysfunctions comparable to those observed in Phenotype A. Consequently, women with Phenotype B are also considered to be at high risk of metabolic syndrome and require careful metabolic assessment, including evaluation of glucose tolerance and lipid profiles [1, 2].

By contrast, Phenotype C, characterized by hyperandrogenism and polycystic ovarian morphology with relatively preserved ovulation, is commonly referred to as the ovulatory phenotype. This phenotype exhibits a distinct reproductive and endocrine profile when compared with the anovulatory forms of the syndrome. Although ovulatory function is better preserved, women with Phenotype C may still experience important metabolic challenges related to androgen excess, even if these abnormalities are generally less severe than those seen in Phenotypes A and B [2, 12].

Phenotype D, defined by ovulatory dysfunction and polycystic ovarian morphology without hyperandrogenism, is often regarded as the mildest and at the same time one of the most controversial phenotypes of polycystic ovary syndrome. It is associated with the least severe hormonal and metabolic profile among the classical phenotypes [2, 12]. Nevertheless, its biological distinctiveness and diagnostic legitimacy remain the subject of ongoing debate, particularly because it appears to carry fewer metabolic risks than the hyperandrogenic phenotypes [1].

When these phenotypes are compared, important differences become evident across menstrual, endocrine, morphological, metabolic, and reproductive domains. Phenotypes A and B are characterized by significant menstrual irregularities as a consequence of ovulatory dysfunction, whereas Phenotype C tends to maintain more regular cycles. Hyperandrogenism is a defining feature of Phenotypes A, B, and C, while it is absent in Phenotype D. Regarding ovarian morphology, polycystic ovarian morphology is present in Phenotypes A, C, and D, but absent in Phenotype B [2, 11]. From a metabolic perspective, Phenotypes A and B are associated with the highest risks, particularly in relation to insulin resistance and the increased prevalence of metabolic syndrome [12]. Fertility-related outcomes also differ among phenotypes, with Phenotype C potentially showing more favorable reproductive outcomes because of its relatively preserved ovulation [2].

Limitations of the Rotterdam Phenotypic Model

A major limitation of the Rotterdam phenotypic model is the marked heterogeneity that persists within each phenotype. Patients classified under the same phenotype may still exhibit substantial differences in clinical symptoms and metabolic risks, which creates important challenges for treatment and management strategies [1, 2]. In addition, the expression of endocrine, metabolic, and reproductive abnormalities is often inconsistent, making it difficult to fully capture the spectrum of the disorder within a single phenotypic category [3]. This lack of uniformity becomes even more pronounced when differences across age groups and ethnic backgrounds are considered, further complicating the consistency of phenotypic classification [13].

Another important weakness of the Rotterdam model is its insufficient prognostic precision. The classical phenotypes alone do not accurately predict long-term metabolic outcomes, including the future development of diabetes or cardiovascular disease [3, 14]. Likewise, their ability to distinguish future reproductive outcomes remains limited, even though this information is essential for counseling and clinical decision-making [6]. The model is also limited in its capacity to forecast the disease trajectory across a woman's life course, despite the fact that such longitudinal understanding is crucial for long-term health planning [15].

Closely related to this issue is the fact that the Rotterdam classification is essentially static rather than dynamic. It does not adequately account for changes in phenotype expression over time that may occur as a result of age, weight variation, treatment, or reproductive stage [1, 5]. The presentation of polycystic ovary syndrome can differ considerably between adolescents, women of reproductive age, and perimenopausal women, which underscores the need for a more flexible and dynamic classification system [15]. For this reason, a longitudinal approach is needed rather than a purely cross-sectional model, so that the evolving nature of the disorder can be better understood and represented [16].

The Rotterdam framework is also limited by its overreliance on descriptive criteria. Its emphasis remains focused on visible diagnostic traits rather than on the biological mechanisms that drive the syndrome, such as insulin resistance and inflammation [2, 17]. Furthermore, it does not adequately integrate broader systemic disease burdens, including adipose tissue dysfunction and genetic predisposition, both of which are important for a more comprehensive understanding of polycystic ovary syndrome [13]. As a consequence, the model falls short of representing the full spectrum of the syndrome as a systemic disorder rather than an exclusively reproductive condition [5].

The debate regarding non-hyperandrogenic presentations remains one of the most controversial aspects of the Rotterdam classification. There is persistent uncertainty as to whether all Rotterdam-defined phenotypes truly share the same core disorder, particularly in the case of Phenotype D, which lacks hyperandrogenism [16]. This has led to questions about whether Phenotype D should be considered a milder form of polycystic ovary syndrome or a separate entity altogether, an issue that may have important implications for future revisions of diagnostic frameworks [3]. This debate reinforces the need for a more nuanced understanding of phenotypic diversity and its implications for both diagnosis and treatment [6].

Pathophysiological Basis of Phenotypic Diversity

Insulin resistance and hyperinsulinemia represent central components in many patients with polycystic ovary syndrome and play a major role in aggravating both hyperandrogenism and ovulatory dysfunction [18, 19]. In this context, hyperinsulinemia enhances ovarian androgen production, thereby contributing directly to the hyperandrogenic state that characterizes many presentations of the disorder [11]. Moreover,

insulin resistance is strongly associated with obesity, metabolic syndrome, and glucose intolerance, all of which are particularly prevalent in Phenotypes A and B of polycystic ovary syndrome [2, 3].

Alongside these metabolic alterations, ovarian dysfunction and androgen excess are fundamental elements in the pathophysiology of phenotypic diversity. Hyperactivity of theca cells promotes increased androgen synthesis, which constitutes a hallmark of polycystic ovary syndrome [11]. At the same time, altered folliculogenesis and failure of dominant follicle selection contribute to anovulation and to the development of polycystic ovarian morphology [20]. These mechanisms are especially pronounced in hyperandrogenic phenotypes, which tend to exhibit more severe metabolic disturbances than other forms of the syndrome [3].

Neuroendocrine dysregulation also contributes significantly to the heterogeneity of polycystic ovary syndrome. In certain subgroups, abnormal gonadotropin pulsatility has been observed, particularly in the form of excess luteinizing hormone drive [20]. This dysregulation alters hypothalamic-pituitary signaling and ovarian steroidogenesis, thereby adding further complexity to the clinical and biological profile of the disorder [21].

In parallel, adipose tissue dysfunction plays an important role in worsening the endocrine and metabolic abnormalities associated with polycystic ovary syndrome. Visceral adiposity has been shown to exacerbate these disturbances, while imbalance in adipokines and altered energy homeostasis further contribute to phenotype severity [2, 11]. However, although obesity is a common feature in many affected women, it is not universally present across all phenotypes, which reinforces the heterogeneous nature of the syndrome [3].

Inflammatory and oxidative pathways add another layer to this pathophysiological complexity. Chronic low-grade inflammation is now recognized as an important component of polycystic ovary syndrome pathophysiology. In addition, a potential bidirectional relationship has been suggested between inflammation and insulin resistance, indicating that each process may intensify the other. Emerging evidence further suggests that oxidative stress may also participate in disease progression and contribute to the persistence of metabolic and endocrine abnormalities [21, 22].

Genetic, epigenetic, and developmental influences help explain why the syndrome can manifest in different phenotypic forms. Familial clustering and heritable susceptibility strongly support a genetic basis for polycystic ovary syndrome [20]. Beyond this, epigenetic programming and the interaction between genes and environmental exposures appear to be crucial in shaping phenotype expression [23]. Consistent with this, genome-wide association studies have identified susceptibility loci related to insulin signaling and steroidogenesis, further supporting the concept that phenotypic diversity in polycystic ovary syndrome reflects complex biological interactions rather than a single uniform mechanism [21].

Emerging Phenotypic Models Beyond Rotterdam

Beyond the classical Rotterdam phenotypes, emerging approaches have proposed broader subclassifications that better reflect the metabolic, reproductive, hormonal, morphologic, and psychosocial heterogeneity of polycystic ovary syndrome. Among these, metabolic phenotypes have gained particular relevance. Insulin-resistant and insulin-sensitive presentations represent an important distinction, since insulin resistance is a common feature in polycystic ovary syndrome and contributes substantially to metabolic syndrome and type 2 diabetes mellitus. In this regard, hyperandrogenic phenotypes are especially associated with insulin

resistance, even independently of obesity [3, 11]. A related distinction is observed between obese and lean polycystic ovary syndrome. Patients with obesity tend to exhibit higher insulin resistance and more adverse lipid profiles than their lean counterparts, although lean patients may still present with elevated luteinizing hormone/follicle-stimulating hormone ratios and important metabolic abnormalities [24]. Likewise, low-risk and high-risk cardiometabolic groups have been described, with phenotypes characterized by hyperandrogenism and ovulatory dysfunction showing greater susceptibility to metabolic disorders and therefore requiring more targeted surveillance [12]. For this reason, metabolic stratification may be especially useful in guiding long-term monitoring and individualized treatment strategies [2].

Reproductive phenotypes provide another important framework for understanding the diversity of the syndrome. A predominantly anovulatory phenotype is characterized by chronic anovulation and frequently requires fertility treatment as part of clinical management [1]. Closely related to this is the subfertility-dominant phenotype, in which impaired fertility is a central concern and responses to assisted reproductive technologies may vary considerably between patients [14]. In contrast, some women present with an ovulatory but hyperandrogenic phenotype, maintaining relatively regular ovulation while still experiencing manifestations of androgen excess such as hirsutism. In addition, phenotypes defined by response to assisted reproductive technologies have also been proposed, since metabolic syndrome has been identified as a predictor of adverse outcomes in this setting, emphasizing the importance of phenotype-specific reproductive management [1, 14].

Hyperandrogenic subtypes further illustrate the biological complexity of polycystic ovary syndrome. In some patients, androgen excess appears to be predominantly ovarian in origin, a pattern that has been linked to increased metabolic risk and reproductive dysfunction. In others, adrenal-predominant androgen excess may play a more relevant role, although this presentation is less common it still contributes to the clinical manifestations of the syndrome. A mixed-source androgen excess pattern, involving both ovarian and adrenal contributions, can also occur and may further complicate the clinical picture [11]. Across these subtypes, the manifestations of androgen excess, including hirsutism, acne, and alopecia, vary widely among patients and can have a substantial impact on quality of life [1].

Morphologic and ovarian reserve-related phenotypes also deserve consideration. Differences in follicle number and ovarian volume, as assessed by ultrasound, remain central to morphological characterization and continue to serve as important diagnostic elements. In parallel, Anti-Müllerian hormone has emerged as a surrogate marker of ovarian reserve and may also contribute to more refined phenotype differentiation, particularly when combined with other endocrine and clinical variables [2].

In addition to endocrine and reproductive dimensions, psychometabolic and quality-of-life phenotypes have become increasingly relevant. Polycystic ovary syndrome is associated with higher rates of anxiety, depression, and body image distress, and these psychological burdens may be more pronounced in certain phenotypic presentations. Therefore, the integration of mental health assessment into the management of polycystic ovary syndrome is essential for truly comprehensive care and for a more complete understanding of disease burden beyond biochemical and reproductive abnormalities [1].

Data-driven and cluster-based phenotypes represent one of the most promising emerging approaches. Statistical clustering methods have identified subgroups that are not adequately captured by traditional diagnostic criteria,

thereby offering the possibility of a more biologically coherent subclassification. These approaches allow the separation of reproductive, metabolic, and mixed presentations, which may improve understanding of the syndrome's heterogeneity and provide a stronger basis for personalized treatment strategies [25].

Clinical Relevance of Advanced Phenotyping

Advanced phenotyping has important implications for metabolic risk assessment in polycystic ovary syndrome, particularly because not all phenotypes carry the same degree of cardiometabolic burden. Phenotypes A and B, which are characterized by hyperandrogenism and ovulatory dysfunction, are consistently associated with higher metabolic risks, including insulin resistance, type 2 diabetes, and dyslipidemia. These phenotypes tend to show higher body mass index, greater waist circumference, and increased Homeostatic Model Assessment for Insulin Resistance scores when compared with other phenotypes, indicating a greater need for early metabolic screening and timely intervention. In contrast, metabolic risk varies substantially across the phenotypic spectrum, making phenotype-specific screening protocols especially relevant. For example, Phenotype D, which lacks hyperandrogenism, generally presents with a milder metabolic profile and may therefore require less intensive monitoring than the more severe hyperandrogenic forms [2, 3, 12].

Beyond metabolic surveillance, advanced phenotyping also has major implications for reproductive health. A more refined phenotypic assessment allows for better estimation of ovulatory status and fertility potential, which are central concerns in the management of many patients with polycystic ovary syndrome. Although Phenotype C is considered ovulatory and hyperandrogenic, these patients may still face fertility-related difficulties due to associated metabolic abnormalities. Understanding the specific phenotype may help predict the response to ovulation induction strategies and improve the assessment of risks such as miscarriage and pregnancy complications. In this regard, hyperandrogenic phenotypes appear to be particularly vulnerable to adverse reproductive outcomes [1, 2, 18].

Phenotypic characterization is also valuable for the evaluation of androgen-related manifestations. It enables a more precise assessment of symptoms such as hirsutism, acne, and alopecia, which may vary considerably among patients even when their reproductive profiles appear similar [11, 17]. This distinction is clinically relevant because phenotypes with comparable ovulatory patterns may still differ greatly in their androgenic burden, thereby influencing both symptom severity and therapeutic priorities. As a result, antiandrogenic treatment strategies can be tailored according to the specific androgenic profile of each phenotype, improving symptom control while also helping reduce the risk of associated metabolic complications [3, 11].

The implications of advanced phenotyping also extend across different age groups. In adolescents, diagnosis can be especially challenging because physiological insulin resistance during puberty and irregular menstrual cycles may overlap with features suggestive of polycystic ovary syndrome, increasing the risk of misdiagnosis if careful phenotypic assessment is not performed [18]. At the same time, phenotypic expression is not static across the lifespan. Clinical presentations may vary during the reproductive years and can change further during the menopausal transition, which means that ongoing reassessment is necessary to adapt management strategies over time [26].

Taken together, these considerations highlight the importance of multidisciplinary care in polycystic ovary syndrome. Effective management requires the integration of gynecology, endocrinology, dermatology, nutrition, and mental health services in order to

provide comprehensive care tailored to the dominant phenotype. In addition, phenotype-based counseling may help patients better understand their condition and the risks associated with their specific presentation, thereby supporting informed decision-making and improving adherence to management plans [1, 18].

Toward Precision Medicine in Polycystic Ovary Syndrome

The transition from criterion-based grouping to mechanism-based classification represents an important conceptual shift in the understanding of polycystic ovary syndrome. Traditional classification systems, such as the Rotterdam criteria, categorize the syndrome into phenotypes according to clinical features including hyperandrogenism, ovulatory dysfunction, and PCOM [1, 2]. Although this framework has been useful for diagnosis, it remains primarily descriptive. In contrast, mechanism-based classification seeks to identify distinct subtypes by considering the underlying biological processes involved in the disorder, including genetic, hormonal, and metabolic factors [17]. This broader approach may allow for more accurate risk stratification and more tailored therapeutic interventions, thereby addressing the marked heterogeneity that characterizes polycystic ovary syndrome [6].

Within this context, the integration of multiple clinical domains has become increasingly important. Endocrine, metabolic, reproductive, and psychological dimensions are closely interconnected in polycystic ovary syndrome and collectively influence both its clinical presentation and progression [11]. Considering these domains together may facilitate the identification of specific subtypes with distinct clinical outcomes, including different levels of metabolic risk or varying reproductive challenges [12]. At the same time, psychological factors, particularly the impact of the syndrome on mental health, are increasingly recognized as major components of disease burden, which supports their inclusion in comprehensive management strategies [1].

A refined classification system also depends on the use of biomarkers capable of capturing these multidimensional differences. Hormonal markers such as testosterone and sex hormone-binding globulin are important for distinguishing between phenotypic expressions of the syndrome [2]. In parallel, metabolic markers, including measures of insulin resistance and lipid profiles, help identify subtypes with greater cardiometabolic risk [17]. Inflammatory markers such as C-reactive protein and interleukin-6 provide additional insight into the inflammatory component of the disorder [2]. Likewise, ovarian reserve markers, particularly Anti-Müllerian hormone, together with imaging techniques, contribute to a more precise understanding of reproductive potential and ovarian morphology. Future diagnostic panels may combine these biomarkers to provide a multidimensional view of polycystic ovary syndrome and thereby improve diagnostic precision [6].

In addition to biomarkers, omics and systems biology have contributed substantially to the move toward a more biologically informed classification. Genomics and transcriptomics have identified susceptibility loci and gene clusters associated with polycystic ovary syndrome traits. At the same time, proteomics and metabolomics have provided insight into the biochemical pathways involved in the syndrome, revealing potential therapeutic targets and helping to clarify its biological complexity [11]. These technologies may also uncover hidden subgroups within polycystic ovary syndrome, which could support more personalized treatment strategies [2].

This evolving classification paradigm has direct therapeutic implications. Treatment may be better tailored according to the dominant clinical pattern, whether metabolic, reproductive, or hyperandrogenic [12]. In this way, lifestyle interventions, insulin-sensitizing therapies, and

ovulation induction strategies may be individualized according to the characteristics of each subtype [1]. Such personalized approaches may reduce the risks of overtreatment and undertreatment, while improving overall patient outcomes [6].

Despite these advances, important challenges remain in the implementation of refined phenotypic models. One major obstacle is the lack of universal consensus regarding new classification systems, which complicates their adoption in routine clinical practice. In addition, access to advanced biomarkers and molecular tools is not uniform across settings, limiting the broader application of these approaches. Translating complex subclassifications into practical and efficient clinical workflows continues to be a significant challenge [6, 17].

Conclusions

Polycystic ovary syndrome is a highly heterogeneous disorder whose classical Rotterdam phenotypes are useful for diagnosis but insufficient to fully capture its metabolic, reproductive, hormonal, and psychological complexity.

The hyperandrogenic phenotypes, particularly Phenotypes A and B, carry the greatest metabolic and reproductive burden, whereas non-hyperandrogenic presentations tend to be milder but remain controversial in terms of their biological distinctiveness and diagnostic validity.

Emerging mechanism-based and biomarker-supported classification models may improve prognostic stratification and individualized management, although their incorporation into routine clinical practice is still limited by the lack of consensus and practical implementation challenges.

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