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Rethinking Polycystic Ovary Syndrome: Why Metabolic Subtyping Must Supersede the Rotterdam Criteria in Clinical Practice

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Opinion

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Abstract

Polycystic Ovary Syndrome (PCOS) is the most common endocrinopathy affecting reproductive-aged women, with a global prevalence exceeding 10% to 15%. For over two decades, clinical diagnosis and management have been anchored in the 2003 Rotterdam consensus criteria, which define PCOS through arbitrary combinations of oligo/anovulation, clinical/biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound. In this opinion piece, I argue that the Rotterdam framework has become an intellectual and clinical bottleneck. By treating PCOS predominantly as a gynecological ovulatory defect rather than a systemic metabolic and neuroendocrine disorder, clinicians frequently overlook profound underlying insulin resistance, visceral adiposity, chronic low-grade inflammation, and premature cardiovascular risk. Cluster analyses and genomic studies now delineate at least two biologically distinct subtypes: a 'metabolic' subtype driven by severe hyperinsulinemia and a 'reproductive' subtype characterized by elevated LH and SHBG levels with normal BMI. Transitioning to a metabolic subtyping paradigm will enable personalized, mechanism-driven therapeutics—including early deployment of GLP-1/GIP receptor co-agonists, inositols, and lifestyle medicine—overcoming the reductionist reliance on oral contraceptives.

Keywords: Polycystic Ovary Syndrome; Rotterdam Criteria; Metabolic Subtyping; Insulin Resistance; GLP-1 Receptor Agonists; Precision Medicine

Abbreviations

PCOS: Polycystic Ovary Syndrome; PCOM: Polycystic Ovarian Morphology; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; GLP-1: Glucagon-Like Peptide-1; GIP: Glucose-Dependent Insulinotropic Polypeptide; COCPs: Combined Oral Contraceptive Pills.

The 20-Year Hegemony of the Rotterdam Consensus

In 2003, the Rotterdam consensus broadened the diagnostic threshold for Polycystic Ovary Syndrome (PCOS) by requiring the presence of any two out of three criteria: oligo/anovulation, hyperandrogenism, and polycystic ovarian morphology (PCOM) on ultrasound [1]. While this successfully expanded research cohorts, it created an extraordinarily heterogeneous diagnostic umbrella (Phenotypes A, B, C, and D) grouping fundamentally different biological entities under a single diagnostic label [2].

In routine clinical practice, a lean 19-year-old athlete with irregular menses and multi-follicular ovaries on ultrasound (Phenotype D) is diagnosed with the exact same condition as a 32-year-old woman with severe acanthosis nigricans, morbid visceral adiposity, hyperinsulinemia, and

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hirsutism (Phenotype A) [3]. This one-size-fits-all approach is no longer tenable in the era of precision medicine.

The Metabolic Blindspot of Gynecological Reductionism

The fundamental flaw of the current paradigm is treating PCOS as a pelvic disorder rather than a systemic metabolic endocrinopathy. Up to 70% to 80% of women with classic PCOS exhibit profound intrinsic insulin resistance independent of body mass index (BMI) [4,5]. Compensatory hyperinsulinemia directly stimulates the ovarian theca cells to overproduce androgens and suppresses hepatic Sex Hormone-Binding Globulin (SHBG) synthesis, driving a vicious hyperandrogenic cycle [6].

By reducing management to the reflexive prescription of combined oral contraceptive pills (COCPs) to induce artificial withdrawal bleeds, clinicians mask the underlying metabolic pathology. In many patients with underlying dysglycemia, standard second- and third-generation progestins can exacerbate insulin resistance and elevate long-term risks for Type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) [7,8].

Evidence for Distinct Biological Clusters

Recent large-scale unsupervised cluster analyses and genome-wide association studies (GWAS) have demonstrated that PCOS segregates into at least two distinct biological subtypes:

- The Metabolic Subtype (approx. 50-60%): Characterized by high BMI, elevated fasting insulin, severe HOMA-IR, low SHBG, and high visceral fat. These patients carry substantial risks for metabolic syndrome and cardiovascular events.
- The Reproductive Subtype (approx. 30-40%): Characterized by normal BMI, elevated luteinizing hormone (LH), normal fasting insulin, and high anti-Müllerian hormone (AMH). These patients present predominantly with ovulatory dysfunction and neuroendocrine axis dysregulation [9,10].

A Call for Mechanism-Driven Precision Therapeutics

I propose that clinical guidelines must immediately retire the binary Rotterdam diagnosis in favor of a stratified metabolic-reproductive scoring framework. Every woman presenting with suspected PCOS should undergo mandatory baseline metabolic profiling, including a 2-hour 75g oral glucose tolerance test with insulin curves, lipid subfractions, and liver transaminases.

For women with the metabolic subtype, frontline therapy must pivot from symptom masking to metabolic restoration. This includes early integration of insulin sensitizers (Metformin, Myo-inositol/D-chiro-inositol in a 40:1 ratio) and modern incretin-based therapies (GLP-1 and GLP-1/GIP dual agonists like semaglutide and tirzepatide), which have demonstrated remarkable efficacy in reversing both hyperandrogenism and restoring spontaneous ovulatory cyclicity [10].

Women deserve diagnostic precision, not a catch-all label that overlooks their lifelong cardiometabolic health.

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