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A Review of the Predictive Roles of the Hormonal Panel and the Essential Evaluation and Phenotyping of Polycystic Ovarian Syndrome

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ABSTRACT:

Menstrual abnormalities, polycystic ovaries, and hyperandrogenism are some of the clinical signs of Polycystic Ovarian Syndrome (PCOS), a complicated endocrine condition that affects women of reproductive age. Despite being common and having an effect on women's health, little is known about the pathophysiology of PCOS. This review addresses information gaps and emphasizes the complex character of PCOS etiology by offering a thorough critical appraisal of the body of existing literature. Gonadotropins, ovarian and adrenal androgens, sex hormone-binding globulin (SHBG), anti-Müllerian hormone (AMH), and tests that rule out other disorders (such as TSH, prolactin, and 17-hydroxyprogesterone) are all part of the "hormonal panel" for PCOS. Evidence-based guidelines have improved diagnostic and therapy routes over the past decade and have considered the interpretation of certain analytes, including AMH. In addition to highlighting the benefits and limitations of key biomarkers and offering useful testing algorithms based on the 2023 International Evidence-based PCOS Guideline and recent systematic reviews, this review compiles the most recent data on the diagnostic, phenotyping, and prognostic roles of the hormonal panel in PCOS.

Introduction:

A wide range of physical, emotional, and social well-being related to a woman's reproductive system and processes are included in her reproductive health. From youth to maturity and across the several phases of reproductive development, it encompasses the comprehensive care and assistance required to sustain good reproductive function throughout a woman's life [1]. Menstrual health, fertility, prenatal care, and mother care are important facets of female reproductive health. Organ mutilations regulated by estrogen, hormonal abnormalities, and diseases including endometriosis, polycystic ovary syndrome (PCOS), fibroids, and malignancies that affect women because of greater exposure to endocrine toxicants are among the reproductive health issues that impact women [2]. A common endocrine condition, PCOS, sometimes goes untreated at first. Its prevalence ranges from 5 to 25%, and it causes a number of clinical and metabolic diseases as well as infertility, which puts a financial strain on healthcare [3,4].

Over 116 million women globally (3.4%) suffer from PCOS, according to estimates from the World Health Organization (WHO) [5]. Although there are significant individual variances, hyperandrogenism, irregular menstruation, and varied ovarian cyst sizes are the hallmarks of PCOS. Adolescents who are at high risk for developing a number of comorbidities, such as obesity, type II diabetes, infertility, endometrial dysplasia, cardiovascular illnesses, and mental disorders, are the first to develop this complex syndrome [6,7].

In addition to genetic and epigenetic factors, the pathophysiology incorporates insulin resistance (IR), hyperandrogenism, and altered hypothalamic-pituitary-ovarian transmission. For diagnosis, phenotyping, mimic exclusion, and continued therapy, hormonal testing is crucial [8,9]. The definition of PCOS was broadened by the Rotterdam Consensus in 2003 to encompass any two of [ovulatory dysfunction, hyperandrogenism, and PCOM]. Ultrasound thresholds, teenage diagnosis, and the possibility of AMH replacing PCOM have been the main topics of later updates. In this review, current diagnostic frameworks are outlined; the effectiveness and limitations of the main analytes—AMH, androgen metrics, LH/FSH ratio, SHBG, prolactin, TSH, and 17-hydroxyprogesterone—are evaluated; and a practical interpretive approach is provided for clinical scenarios ranging from adult to adolescent, fertility to metabolic emphasis.

Methods:

How to Locate and Select Studies:

Utilizing combinations of polycystic ovarian syndrome OR PCOS AND (androgen OR testosterone OR DHEAS OR androstenedione OR anti-Müllerian hormone OR AMH OR LH OR FSH OR LH/FSH ratio OR SHBG OR insulin resistance OR prolactin OR TSH OR 17-hydroxyprogesterone), we performed a narrative search of PubMed and Scopus until August 15, 2025, applying filters for human studies and English language. We prioritized large cohort studies, meta-analyses, systematic reviews, and guidelines. We manually went through the citation lists of significant articles. We excluded abstracts without full text, populations that did not meet the usual definitions of PCOS, and non-peer-reviewed literature.

The function of the hormonal panel and diagnostic frameworks, from the NIH (1990) to Rotterdam (2003) to the 2023 Guideline

After ruling out other relevant disorders, the NIH 1990 classification concentrated on hyperandrogenism and ovulatory failure. The classification was expanded by Rotterdam (2003) to include PCOM as one of three criteria, requiring the presence of any two in order to make a diagnosis. Despite normal ovulatory patterns, this inclusion produced phenotypes with PCOM without hyperandrogenism or hyperandrogenism with PCOM. Ultrasound thresholds were clarified in the 2023 International Guideline, which also stated that high AMH might be used in place of PCOM in adults (with caution in youth). Which hormone tests are prioritized and how they are interpreted are directly impacted by these modifications.

According to the guideline, PCOS in teenagers should only be identified when there is both clinical or biochemical hyperandrogenism and chronic ovulatory dysfunction; because of developmental variability, reliance on PCOM or AMH should be avoided [10,11]. AMH is not yet approved as a stand-alone diagnostic criterion, hence the focus in teens is on trustworthy indicators of hyperandrogenism and exclusionary testing. This has immediate ramifications for the hormonal panel.

Elevated levels of total testosterone (TT), computed free testosterone (cFT), free androgen index (FAI), androstenedione (A4), or, less frequently, dehydroepiandrosterone sulfate (DHEAS) can be used to diagnose biochemical hyperandrogenism. While A4 is often informative and DHEAS is raised only in a fraction, suggesting adrenal contribution, high-quality evidence suggests that TT and cFT/FAI are the most useful diagnostic analytes. The assay's quality (LC-MS/MS for TT, for instance) and the phase or time of day are crucial.

- Diagnostic accuracy: TT, cFT, FAI, and, in certain studies, A4 have better diagnostic efficacy for biochemical hyperandrogenism than DHEAS and DHT, according to a 2024 systematic review that was intended to inform the International Guideline.
- Clinical nuance: The role of 17-hydroxyprogesterone as a diagnostic exclusion test is highlighted by the necessity of looking into adrenal tumors or non-classic congenital adrenal hyperplasia (CAH) in response to a marked increase in DHEAS levels.

Results:

People with IR, obesity, and hyperinsulinemia frequently have low SHBG, which increases FAI and free androgen activity. SHBG is not a standalone diagnostic test; rather, it contextualizes androgen bioavailability and cardiometabolic risk. Integrating SHBG with TT (to calculate FAI) makes interpretation easier because recent studies show that SHBG varies with insulin sensitivity phenotypes [12].

Due to pulsatile secretion and test-to-test variations, the long-taught LH/FSH ratio >2:1 does not have the sensitivity and specificity that were previously believed. Although certain groups have greater ratios due to heightened LH levels, this ratio should not be used as the only diagnostic criterion. On the other hand, it can intensify an anovulation and hyperandrogenism pattern. AMH: From an indicator of ovarian reserve to a PCOS warning indication [13-16].

AMH is released by granulosa cells found in pre-antral and tiny antral follicles. Serum AMH levels are typically two to three times higher than usual in women with PCOS. This is a result of their granulosa cells not functioning properly and their increased number of tiny follicles.

Mechanistic investigations correlate AMH with changed follicle selection and presumably with GnRH neural activity, supporting its participation in the anovulatory phenotype [18].

Consolidated for the 2023 Guideline, there is growing evidence that AMH can help with adult diagnosis and could take the place of PCOM in situations where validated thresholds and high-quality assays are available. According to meta-analytic estimations, thresholds for adult diagnosis should be about ~4.7 ng/mL; however, cut-offs vary by demographic and are based on assay and age. AMH levels alone should not be used to diagnose adolescents [19-22].

AMH may be used to monitor the effectiveness of specific therapy and is associated with ovulatory status. Although there is preliminary evidence that metabolic treatments (such as metformin in IR-predominant phenotypes) may affect AMH levels, clinical outcomes are still the main emphasis, hence this is not yet a standard monitoring goal [23].

IR interacts with hyperandrogenism in both directions and is common in PCOS phenotypes. Insulin resistance increases free androgens by lowering SHBG in the liver. In addition to increasing theca cell steroidogenesis, high insulin levels can alter the function of gonadotropins. Although fasting insulin

and HOMA-IR do not diagnose PCOS, they do stratify metabolic risk and provide context for increased FAI and low SHBG. Weight/waist measurement, fasting lipid profile, and OGTT or HbA1c should all be part of the first care provided by the clinician [24-26].

Other causes of hyperandrogenism and anovulation must be ruled out by the hormonal panel in PCOS.

- **TSH:** Primary thyroid disease might mimic irregular menstruation.
- **Prolactin:** Significant increases in this hormone suggest pituitary disease; hyperprolactinemia can cause oligoamenorrhea.
- **17-hydroxyprogesterone:** Non-classic CAH may be indicated by high morning follicular-phase levels (>200 ng/dL; assay-specific).
- **Cushing's/androgen-secreting tumors:** Targeted testing and imaging are required if there are clinical signs of concern or noticeably high androgen levels. These are emphasized in current guidelines to prevent overdiagnosis of PCOS.

Phenotypes have different biochemical profiles. Compared to "non-hyperandrogenic" phenotypes (C/D), classic hyperandrogenic, anovulatory phenotypes (A/B) typically exhibit higher TT/FAI and occasionally higher LH. AMH is most strongly correlated with the severity of anovulation and is generally higher across phenotypes.

Before diagnosing an adolescent with both prolonged ovulatory failure and hyperandrogenism, it is crucial to rule out other explanations because physiologic anovulation and acne/hirsutism can occur together with normal puberty. At this age, PCOM and AMH are not advised as first-line tests.

BMI and ethnicity have an impact on androgen and SHBG levels; independent of absolute TT, obesity raises FAI and lowers SHBG, which may indicate hyperandrogenism. This highlights how important it is to combine metabolic profile and clinical assessment with biochemical testing.

Combining Everything: A Practical Hormonal Testing Method

1. Confirm the clinical situation (metabolic focus versus fertility; adult versus youth).
2. TT (ideally LC-MS/MS), SHBG (to determine FAI/cFT), ± A4, prolactin, TSH, and morning 17-OHP are the first-line labs for adults (if androgens are high or the risk is high). Consider DHEAS if you believe the adrenal gland is the cause.
3. Consider AMH in adults when tests and thresholds have been validated, particularly in cases when ultrasonography is unclear or unavailable. Avoid using AMH with teenagers.
4. The LH/FSH ratio is merely optional context; it is not a diagnostic tool.5. A metabolic work-up to determine the level of cardiometabolic risk SHBG/FAI signifies and what low it is (OGTT or HbA1c, lipids, blood pressure, anthropometrics).

AMH signaling is implicated in both follicular arrest and GnRH activity, according to preclinical and translational research. An AMH-blocking antibody has shown promising pathophysiologic reversal in early investigations, suggesting the possibility of new disease-modifying treatments in the future. It emphasizes how a "diagnostic" hormone may develop into a therapeutic target, even though it is not currently a clinical norm. Although an excessive number of follicles is indicated by a very high AMH level in PCOS, this does not guarantee a live birth by assisted reproduction. Indeed, after fresh embryo transfer, a very high AMH level may indicate issues with the quality of folliculogenesis by increasing the risk of miscarriage and decreasing the possibility of a live birth. Weight control and insulin-sensitizing techniques remain crucial because IR interacts with excessive androgen. The effects of dietary patterns, such ketogenic diets, on metabolism and reproduction are being studied. The results highlight the metabolic underpinnings of the hormonal panel, despite the fact that they are variable and dependent on adherence.

Hormonal testing's limitations in PCOS Assay variability: When available, LC-MS/MS is preferred over immunoassays, which have the potential to overestimate or underestimate TT at low female ranges.

- Biologic variability: Interpretation is influenced by cycle phase, diurnal changes, and pulsatility (e.g., LH).
- Phenotypic heterogeneity: Clinical symptoms are crucial because not all PCOS cases show overt biochemical hyperandrogenism.
- Age and life stage: AMH is not a valid diagnostic marker in adolescents, and ultrasonography thresholds and AMH must be read in light of age.

Conclusion

The review makes it quite evident that PCOS is a complicated illness. It is challenging to comprehend and articulate the main mechanism. Because it treats the clinical symptoms rather than the illness, no treatment can be hailed as a panacea. By understanding their mode of action, alternative medications like herbal or medicinal plants should be taken into consideration. More research into the pathophysiology and medications that affect it is necessary to predict the long-term effects on the patient's health. Modifying one's lifestyle may help reduce the symptoms associated with PCOS.

The modern hormonal panel for PCOS is based on exclusionary tests (TSH, prolactin, 17-OHP), contextual indicators (SHBG, LH/FSH as corroborative data), AMH (in adults with specified thresholds and assays), and accurate androgen evaluation (TT with SHBG-based cFT/FAI; ± A4). It is simpler to

diagnose and arrange care when you use IR, BMI, and phenotypic to help you comprehend the data. The 2023 International Evidence-based Guideline emphasizes the necessity to evaluate metabolic risk and provide specific care for adolescents while tying the diagnostic process to the realities of testing. Future studies are likely to examine hormonal system modification (such as AMH blocking) as a targeted treatment, standardize androgen assays globally, and enhance AMH's clinical cut-offs.

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Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

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Author contributions

Rishad Ahmed: Conceptualization; Formal analysis; Methodology; Writing—original draft; data collection. **Kausik Datta:** Conceptualization; Formal analysis; Methodology; Writing—original draft; data collection. **Mridul Bera:** Conceptualization; Formal analysis; Methodology; Writing—original draft; data collection. **M.G. Alam:** Conceptualization; Formal analysis; Methodology; Writing—original draft; data collection.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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