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POLYCYSTIC OVARIAN SYNDROME UNVEILED: NAVIGATING THE COMPLEXITIES AND IMPACTS ON WOMEN'S REPRODUCTIVE HEALTH

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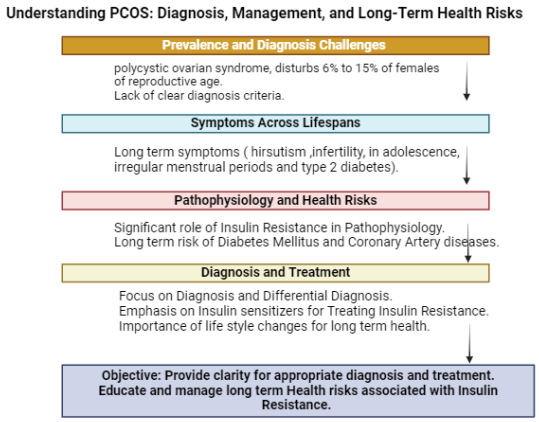
Abstract

PCOS, also known as polycystic ovarian syndrome, disturbs 6% to 15% of females of reproductive age. Many clinicians find it difficult to identify this widespread condition due to the lack of clear diagnostic criteria. Additionally, a patient may present to any number of clinicians due to the disorder's numerous presentations, including internists, family practitioners, nurse practitioners, pediatricians, gynecologists, endocrinologists, or dermatologists. Moreover, a patient's most troubling PCOS symptom may vary over time from hirsutism as an adolescent to sterility as a young mature necessitating visits to multiple doctors along the way. Therefore, it is critical that healthcare providers comprehend not just the specialty-specific management concerns but also the additional health risks associated with these women. Insulin resistance has been found to play a significant role in the pathophysiology of PCOS, highlighting the long-term risks associated with diabetes mellitus and the resulting elevated risk of coronary artery disease. Inconsistent menstruation and hirsutism are no longer considered harmless annoyances. The diagnosis/differential diagnosis and treatment options, the two most perplexing aspects of polycystic ovary syndrome for the practicing provider, will be the main topics of this study. The significance of insulin resistance (IR) and the potential treatment benefit of insulin sensitizers are particularly emphasized. Additionally, the advantage and critical nature of lifestyle changes for these women's long-term health are highlighted. It is believed that more clarity in this area will enable more women to receive the appropriate diagnosis and treatment for their presenting symptoms (hirsutism, irregular menses, etc.) as well as to receive education and care for the long-term health risks of IR.



Keywords: Polycystic ovarian syndrome, Insulin resistance, Hirsutism, and Hyperandrogenism

Introduction

The endocrine metabolic illness known as polycystic ovary syndrome is primarily caused by an excess of androgen synthesis originating from the ovaries and adrenal glands. This excess androgen production leads to changes in the skin, reproductive system, and metabolism (1). A significant proportion of women with normal weight and almost all overweight individuals exhibit resistance to insulin action due to these changes, which are caused by dysfunctional adipose tissue. Despite having a complicated, multifaceted, and variable etiology, it is the furthermost common metabolic endocrinopathy in females of reproductive age. Its prevalence can range from 6% to 15% globally (2).

Definition and Epidemiology

There has been some misunderstanding about its definition since Stein and Leventhal's original description of it, both among women who experience it and among medical professionals who are unfamiliar with it. The term polycystic, which refers to one of the syndrome's effects the radiological appearance of the gonads, where follicles are paused at various maturational stages but are not truly cysts is largely to blame for the confusion (3). This term obscures the syndrome's nature as a metabolic endocrinopathy, which has implications beyond reproduction. (4). The syndrome is defined by this criteria, which is now referred to as classic PCOS, as the presence of clinical and biochemical ovulatory failure as well as excessive androgen (5).

The American Society of Reproductive Medicine and the European Society of Human Reproduction published the Rotterdam criteria in 2003, which were an attempt to reach a consensus on a more inclusive definition that would include women with polycystic ovarian morphology (POM) and ovulatory dysfunction without hyperandrogenism (6).

By this definition, if there are no other medical conditions that could mimic the clinical signs and characteristics of polycystic ovary syndrome, then at least two of the following criteria must be met for a PCOS diagnosis: (a) biochemical hyperandrogenism; (b) ovulatory dysfunction; and (c) POM in transvaginal ultrasonography (7). Furthermore, these women are more likely to experience related metabolic side effects, including glucose intolerance, dyslipidemia, insulin resistance, hypertension, obstructive sleep apnea, non-alcoholic steatohepatitis, and diabetes mellitus (DM).

Irrespective of POM, phenotypes that link ovulatory failure with hyperandrogenism, particularly biochemical ones, present more detrimental clinical and metabolic effects. The ovulatory phenotype is the next most severe phenotype, and the non-hyperandrogenic phenotype is the less acute phenotype from a metabolic standpoint. Therefore, a proper diagnosis and patient phenotyping make it easier to address the cardiometabolic danger that these females face (8).

Etiology and Physiopathology:

a. Family Aggregation

Family aggregation is known to exist in the families of PCOS-affected women, pointing to a potential genetic foundation for the etiopathogenesis of the condition (9). Variability in the disease's phenotypic expression might arise from the interplay between genotype and environment. Since only a small number of genetic variations have been simulated in polycystic ovary syndrome-affected individuals from various populations, the hunt for the genes causing this syndrome has proven fruitless. The primary causes of this failure are the lack of sufficient clinical phenotyping of the patients, the use of various diagnostic criteria that make it challenging to compare data between diverse populations, and the potential for the involved genetic variants to differ based on the ethnic substrate (10). Moreover, non-genotypic spread of a lifestyle may drive this family aggregation rather than genetic factors as shown in table 1. This creates a harmful environment that starts in the womb and leads to metabolic reprogramming that causes, androgen excess and insulin resistance(IR) (11).

Table 1. Phenotypic Classification of PCOS

Phenotypes	Diagnostic Criteria	References
Phenotype 1	Oligoovulation+POM+Hyperandrogenism	(12)
Phenotype 2	Oligo-ovulation + Hyperandrogenism	(13)
Phenotype 3	Hyperandrogenism + POM	(5)
Phenotype 4	POM + Oligo-ovulation	(14)

b. Association between High Testosterone and Insulin Resistance

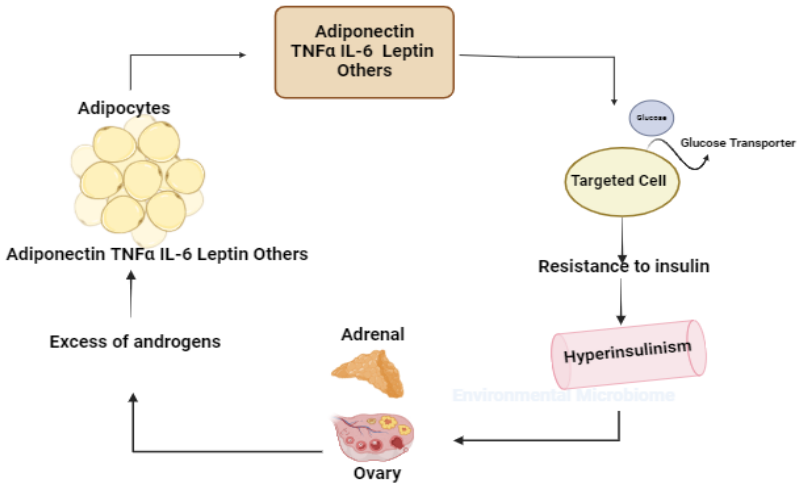
Insulin sensitivity is lesser in hyperandrogenic patients with normal body weight. This is especially true for females with PCOS compared to healthy women. Insulin resistance and compensatory hyperinsulinemia with hyperandrogenism are correlated in both directions (15). On the one hand, insulin promotes hyperandrogenemia by stimulating the luteinizing hormone (LH). About 50% of women with PCOS have altered LH pulsatility due to a combination of hyperandrogenemia and hyperinsulinemia. These detrimental consequences of endogenous hyperinsulinism can also arise in exogenous hyperinsulinism conditions, as demonstrated by a notable proportion of women with type 1 diabetes (16).

The androgen excess that characterizes PCOS also impacts metabolic changes such as insulin resistance, carbohydrate metabolism problems, and central obesity (17). In summary, the pathophysiology of PCOS is a vicious cycle in which an excess of androgens promotes the deposition of visceral and abdominal fat, which in turn promotes the synthesis of androgens in the ovaries and adrenal glands. This process is mediated both through the promotion of insulin resistance and proinflammatory substances and through compensatory hyperinsulinism (18).

c. Polycystic Ovary Syndrome and Its Heterogeneity

Taking everything into account, abdominal obesity's outward manifestation and the degree of insulin resistance will impact PCOS's phenotypic expression. Based on the current scientific evidence, we believe that PCOS arises from a combination of factors, surplus weight and excessive androgen. This theory states that signs of androgen excess can appear even in weak females if the intrinsic defect is severe enough. On the other hand, a small defect in the process of conversion of cholesterol into steroid hormones will only show clinical symptoms when obesity or insulin resistance, are present as shown in Figure 1 (18).

Figure 1. Potential role of inositol in polycystic ovarian syndrome-mediated severe cyclic disruption in endocrinology and obesity.



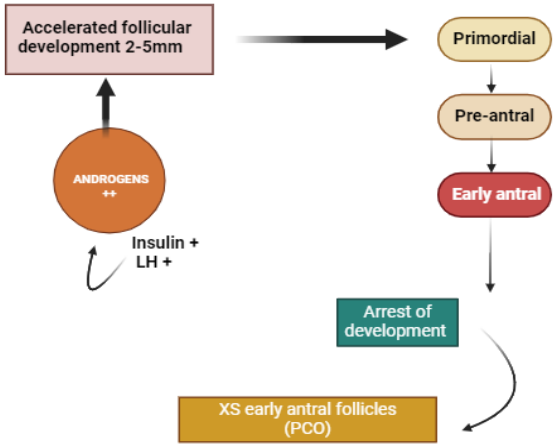
Pathophysiology

The pathophysiology of PCOS involves the following four major abnormalities (19).

a. Abnormal Ovarian Morphology

The polycystic ovary has roughly 6 to 8 times as many pre-antral and tiny antral follicles as a normal ovary. These follicles are susceptible to exogenous follicle-stimulating hormone (FSH), have a sluggish rate of atresia, and stop developing at a size of 2–9 mm. There is always an increased stromal volume, and a total ovarian volume greater than 10 cc is frequently observed (20). An excess of androgens is likely a major contributing factor to the abnormal ovarian morphology as shown in Figure 2. Androgens aid primary follicle development up to the pre-antral and small antral follicle stages. In the case of excess androgens, this process proceeds more quickly than in a healthy ovary. The growth arrest may be caused by excess androgens, in addition to the presence of many factors that impede the endogenous activity of FSH (21). Additionally, excess anti-apoptotic factors, which are also found in excess in PCOS, slow down the turnover of these arrested follicles. These variables could be the cause of the growth arrest. Polycystic ovaries have a distinctive appearance attributed to a combination of several factors (22).

Figure 2. Pathophysiology of Polycystic Ovarian Syndrome.



b. Excessive Ovarian Androgen Production

PCOS is primarily caused by excessive ovarian androgen production. Nearly all of the enzymatic processes in the polycystic ovary that promote the generation of androgens are accelerated. Testosterone production is exacerbated by LH and insulin, both separately and together (19).

c. Hyper-Insulinaemia

In addition to affecting 30-40% of weak females with polycystic ovary syndrome, hyperinsulinemia caused by IR affects about 80% of females with polycystic ovary syndrome and central obesity. This is specific to female PCOS patients and is believed to be caused by a post-receptor abnormality impacting glucose transport. An important aspect of the pathophysiology of anovulation and hyperandrogenism is insulin resistance, which is markedly aggravated by fat. There have also been reports of anomalies in pancreatic beta-cell activity (23).

d. Excessive Serum Concentrations of LH

In single-spot blood tests, approximately 40-50% of polycystic ovary syndrome -affected women exhibit excessive serum concentrations of LH. Lean females are more likely than overweight females to have elevated LH concentrations. FSH action may be intrinsically inhibited, even if serum concentrations of the hormone are frequently within the low normal range. Prolactin levels may be somewhat elevated (24).

Diagnosis and Differential Diagnosis:

According to previous notes, the diagnosis of PCOS is established in the absence of identifiable pituitary and adrenal pathology and is based on hyperandrogenism or persistent anovulation. Table 3 outlines the tests necessary to thoroughly evaluate these possibilities alongside the differential diagnoses of PCOS. It appears that some, but not all, symptoms of PCOS may overlap with these conditions. Examples of conditions that should be ruled out include pregnancy, hyperprolactinemia, and hypothyroidism, all of which can lead to secondary amenorrhea but not hirsutism (25). A comprehensive history and physical examination are necessary to identify any additional symptoms of diseases unrelated to PCOS.

The presence of goiter and symptoms such as increased fatigue, dry skin, and cold intolerance could indicate hypothyroidism. Women with hyperprolactinemia may or may not exhibit galactorrhea. Virilization symptoms indicate markedly higher testosterone levels than those seen in PCOS and may suggest an adrenal or ovarian tumor. Hypertension, broad dorsal cervical fat pads, purple abdominal striae, and a rounded, plethoric face may be more common in patients with Cushing's syndrome. Despite being rare, late-onset congenital adrenal hyperplasia is worth mentioning since clinically, it can resemble PCOS in every aspect (26). One of several enzymatic errors in adrenal steroidogenesis causes congenital adrenal hyperplasia. The classic types of these conditions present with ambiguous genitalia in newborn girls and include complete enzymatic abnormalities (27). Using measurements of the hormone that precedes the enzymatic block, these conditions can be definitively diagnosed. Since 21-hydroxylase deficiency is the most common cause of late-onset congenital adrenal hyperplasia, it is often the only type examined in PCOS differential diagnosis tests (28).

Laboratory Evaluation

Biochemical assessments should exclude the aforementioned conditions and investigate indications of PCOS. Each patient should undergo all tests shown in Table 2. It is important to note that there are various approaches to addressing the challenges associated with direct testing for example, (IR) (29). For simplicity, only the most basic fasting glucose-to-insulin ratio is provided. It is worth noting that the fasting glucose-to-insulin ratio has been primarily studied in obese and lean euglycemic adult white women who are not Hispanic teens, as well as in obese and lean euglycemic adult women who are not Hispanic. In individuals with impaired glucose tolerance , it may not be a

reliable indicator; therefore, testing for IR in non-euglycemic patients may be futile (30). Additionally, it could be argued that none of the IR tests are very sensitive or specific, hence questioning the necessity of any IR tests. However, measuring glucose and lipids while fasting may suffice. Lastly, a 2-hour oral glucose tolerance test is highly beneficial in assessing patients' risk of DM, which can influence treatment decisions. Differential diagnostic tests are listed in table 3. It may also be a stronger predictor of IR than fasting glucose. The interpretation of these laboratory tests involves several nuances that can significantly impact subsequent decisions (31).

Table 2. Diagnostic standards for women with insulin resistance syndrome.

Parameters	Diagnostic Criteria	References
Blood pressure	Greater or equal to 135/85	(32)
Triglycerides	Greater or equal to 150 mg/dL	(33)
Fasting glucose	Greater or equal to 110 mg/dL	(34)
HDL-cholesterol	Less than 50 mg/dL	(32)

Table 3. Screening tests and Differential diagnosis of PCOS from other Gynecological disorders.

Diagnosis	Laboratory test
Ovarian tumor	Total testosterone
Late-onset CAH	17-hydroxyprogesterone
Hypothyroidism	TSH(thyroid stimulating hormone)
Pregnancy	Pregnancy test
Hyperprolactinemia	Prolactin
Late-onset CAH	17-hydroxyprogesterone

1) Testosterone

Given the issues with many tests used to measure free testosterone, a total testosterone measurement is likely more accurate than a free testosterone measurement. In PCOS, testosterone levels could be normal. Most testosterone levels in PCOS will be less than 150 ng/dL (35).

2) Dehydroepiandrosterone-sulfate (DHEA-S)

In PCOS, DHEA-S readings can be slightly increased or normal. When DHEA-S levels exceed 800 µg/dL, an adrenal tumor should be taken into account (36).

3) Prolactin

According to reports, 5% to 30% of PCOS patients have mild hyperprolactinemia. Generally speaking, prolactin levels are only 50% higher than the upper bound of normal. It should be noted that hyperprolactinemia is typically a temporary condition, with approximately 3% to 7% of hyperprolactinemic PCOS patients exhibiting consistently increased prolactin levels (37). This has led to the current belief that hyperprolactinemia and PCOS are separate conditions. Further investigation for additional causes should be conducted if normalization upon resampling does not occur. Polycystic ovaries may be observed on ultrasound in patients with prolactinomas (38).

4) Luteinizing Hormone/Follicle-Stimulating Hormone Ratio

Although not very sensitive or specific, a ratio greater than 2.0 is suggestive of PCOS. Oral contraceptives have an impact on gonadotropin levels (39).

5) Pelvic-ultrasonography

Pelvic ultrasonography can also be very beneficial in the evaluation process; however, over 20% of normal women also have polycystic ovaries, suggesting that the condition is not exclusive to PCOS. In the ultrasound evaluation, the quantity of follicles and ovarian volume are both significant (40).

The confirmative diagnosis of polycystic ovary syndrome is based on the presence of multiple cysts, having a diameter of 02 to 08 mm, or more than 12 follicles, each having diameter of 02 to 09 mm, within an increased quantity of stroma and increased ovarian area or volume. For PCOS diagnosis, these criteria exhibited a 99% specificity and a 75% sensitivity (41).

Treatments:

To prevent or treat metabolic issues, minimize the psycho-emotional effects of percutaneous symptoms of androgen excess, enhance fertility in women who wish to have children, and prevent endometrial hyperplasia in women with severe ovulatory failure (42). Hygienic-dietetic interventions are generally recommended for all patients aiming to address or prevent obesity, sedentary behavior, and smoking. In cases of mild conditions, patients may only require clinical monitoring to ensure that they experience more than 4-6 menstrual cycles annually, which efficiently preserves the endometrium. Conversely, moderate to severe symptoms and indicators will necessitate long-term medication therapy to ensure adequate management (43).

1. Treatment of Androgen Excess

Generally speaking, the recommendation to use dermatology cosmetic methods alongside pharmaceutical treatment varies depending on psychological response and the seriousness of the patient's signs. Dermatological treatment for excessive hairs around the mouth and chin includes techniques such as electrolysis, shaving, waxing, and laser photo depilation, bleaching, or tweezing to remove excessive terminal hair. Symptom management may involve antibiotics or retinoids for acne, and topical minoxidil for hirsutism and alopecia (3). Birth controlling pills containing progestagens with low affinity for androgen receptors or anti-androgenic profiles (such as cyproterone or drospirenone) are preferred systemic treatments. Progestogens like dienogest and norgestimate reduced the risk of coagulation in this population (39). Ethinylestradiol doses at 32–40 μg/day are recommended for teenagers who have not yet touched their peak bone mass (27).

2. Treatment of Ovulatory Dysfunction

Menstrual disruption and subfertility should be considered when treating symptoms related to oligo-anovulation, with treatment tailored to each patient's specific needs. Acute ovulatory problems in females without gestational desire carries a higher risk of developing endometrial cancer and hyperplasia. This risk is particularly pronounced in females with less than normal cycles annually (44). Individuals with mild menstrual problems can be monitored annually, while those with acute menstrual problems require pharmaceutical treatment. For sexually active women without contraindications or who decline other treatments, combining oral contraceptives (OC) is recommended if immediate pregnancy is not desired and psychological or emotional effects are experienced. Other options include cyclical progestogen use to induce menstruation through deprivation, continuous progestogen use, or levonorgestrel-releasing intrauterine devices, especially for patients without excess androgens who do not want OC treatment (45). Initial steps for overweight women with gestational cravings include weight reduction. Additionally, conducting a semen analysis is recommended as a first step in fertility assessment (46).

3. Obesity and Metabolic Complication

Hygienic-dietary guidelines should be the initial treatment approach for all PCOS patients. The objective is to reduce excess weight or maintain a normal weight, thereby improving body fat distribution, excess testosterone levels, and insulin resistance. However, sustaining lifestyle modifications over the long term is often challenging, particularly for individuals with moderate-to-severe obesity (5). Weight reduction following metabolic surgery has been shown to enhance reproductive parameters in females with a body mass index exceeding 35 kg/m^2 (47). However, future pregnancies should be postponed until after the rapid weight loss period following surgery to prevent intrauterine growth constraints due to potential dietary insufficiencies. The signs for bariatric surgery in PCOS patients currently align with those for the general population.

Nevertheless, several anti-obesity medications have been used in PCOS patients. These medications may enhance weight loss when combined with lifestyle modifications (43).

4. Management of Infertility: Treatment by Using Medicines

PCOS contributes to anovulatory infertility in 75% of cases. Additionally, miscarriage rates in the first trimester may range from 30% to 50% in pregnancies that do occur. Effective medical management of infertility in these individuals can bring great satisfaction to both patients and healthcare providers (48). However, addressing infertility can pose challenges, underscoring the importance of teamwork among endocrinologists, gynecologists, and possibly reproductive endocrinologists. This review will not delve deeply into the intricacies of managing infertility in PCOS patients. Instead, it will briefly explore PCOS patients' relative resistance to clomiphene medication, followed by a more comprehensive analysis of the potential benefits of techniques aimed at enhancing insulin sensitivity (49).

a. Clomiphene Citrate

Low doses of clomiphene are generally ineffective for obese women with PCOS; in women weighing over 91 kg, the ovulation rate at 50 mg is barely 20%. Indeed, the amount of clomiphene needed to induce ovulation correlates with the degree of obesity. Multiple gestations may occur more frequently and may have side effects due to the higher doses of clomiphene often required (50).

b. Metformin

Metformin is utilized to address PCOS-related anovulation and decrease insulin and androgen concentrations. This oral biguanide, well-established for hyperglycemia treatment, does not induce hypoglycemia in normoglycemic patients (51). Despite some conflicting data on its efficacy and lack of official licensure for PCOS treatment, metformin is commonly recommended. It can be administered alone or in conjunction with clomiphene to aid PCOS patients in restoring ovulation. Since assessing insulin resistance is challenging and does not consistently predict treatment outcomes, it is not a prerequisite for initiating treatment (52).

Metformin functions as an insulin sensitizer, reducing insulin secretion and resistance, thereby decreasing ovarian androgen production. It also directly impacts ovarian theca cells, diminishing androgen synthesis. Dosage typically ranges from 500–2500 mg daily. A graded initial dose may mitigate gastrointestinal adverse effects affecting 15–20% of patients. In PCOS patients with oligo-anovulation, metformin monotherapy can enhance menstruation frequency and restore ovulation, albeit less effectively than clomiphene alone (53). Controlled studies in non-obese PCOS women have demonstrated significantly improved pregnancy rates with metformin co-treatment during ovarian stimulation in GnRH agonist long protocol or in-vitro fertilization (IVF) procedures, compared to placebo. Metformin usage throughout pregnancy has not shown an increase in congenital malformations, teratogenicity, or adverse fetal effects, suggesting its safety during pregnancy. However, the debate regarding the appropriateness of metformin use during pregnancy remains ongoing (54).

5. Laparoscopic Ovarian Drilling (LOD): An Operative Therapeutic Technique

Bilateral wedge ovarian resection was once the primary diagnostic and therapeutic approach for PCOS. However, its use was discontinued due to a high incidence of pelvic adhesion formation, despite its efficacy in restoring ovulation and facilitating pregnancy for many women (55). Laparoscopic ovarian drilling (LOD) has since revived the operative therapy principle, likely by reducing ovarian mass. During LOD, performed via laparoscopy, the cortex of each ovary is punctured four to ten times at a depth of two to four millimeters. Using bipolar or unipolar electrocautery, it is typically recommended to apply 40 W for 4 seconds for each puncture, although lasers are also an option (56). Electrocautery is preferred for its superior outcomes and lower

adhesion formation rate. Initial reports indicate an 84% ovulation rate and a 56% pregnancy rate within a year of LOD. A significant advantage of LOD for inducing ovulation in PCOS patients is the nearly exclusive occurrence of mono-follicular ovulation, minimizing the risk of multiple pregnancies and eliminating ovarian hyperstimulation syndrome (OHSS). Furthermore, compared to other ovulation induction methods for PCOS, the miscarriage rate following LOD is lower (57).

Conclusion

PCOS stands as the foremost endocrine condition affecting women prior to menopause. Its intricate etiopathogenesis is shaped by diverse factors, encompassing genetic, epigenetic, and environmental influences. Diagnosis hinges on confirming ovulatory failure, biochemical hyperandrogenism, and/or polycystic ovarian morphology (POM), while excluding alternate potential causes for oligo-anovulation and excess androgen symptoms. Treatment aims to ameliorate androgen excess symptoms, ovulatory dysfunction, and preempt or address early metabolic complications. It should be personalized, enduring, and adapted to each patient's individual needs across their lifespan. Timely diagnosis and appropriate management, including lifestyle modifications and/or insulin sensitizers, hold potential to delay or even avert the onset of type 2 diabetes mellitus and associated coronary artery disease risk. PCOS presents as a multifaceted and intricate condition requiring specialized expertise for precise diagnosis and sustained care. This appraisal is anticipated to contribute to the expanding repository of knowledge sought by medical professionals across various specialties in managing these challenging patients.

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