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DIAGNOSIS, PATHOGENESIS, AND MANAGEMENT OF PCOS-RELATED INFERTILITY: A COMPREHENSIVE LITERATURE REVIEW

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Abstract

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine and metabolic disorder affecting women of reproductive age, with a global prevalence estimated between 5% and 20% depending on the diagnostic criteria applied. It is a leading cause of anovulatory infertility and is characterized by a heterogeneous constellation of reproductive, endocrine, and metabolic abnormalities. This literature review synthesizes current evidence on the genetic underpinnings, complex pathogenic mechanisms, and evidence-based management strategies for PCOS-related infertility. Key topics include the polygenic architecture of PCOS, epigenetic and transgenerational transmission, the central roles of hyperandrogenism, insulin resistance, chronic low-grade inflammation, mitochondrial dysfunction, and endoplasmic reticulum stress in disease pathophysiology, as well as the impact of elevated anti-Müllerian hormone and ovarian microenvironment dysregulation. Management strategies encompass lifestyle modification, pharmacological ovulation induction with clomiphene citrate and letrozole, metformin and GLP-1 receptor agonist therapy, gonadotropin protocols, and advanced assisted reproductive technologies including IVF with tailored stimulation. Understanding the multidimensional nature of PCOS is critical for optimizing fertility outcomes.

Keywords

polycystic ovary syndrome, PCOS, infertility, genetics, hyperandrogenism, insulin resistance, ovulation induction, IVF, assisted reproduction

1. Introduction

Polycystic ovary syndrome (PCOS) is a complex, heterogeneous endocrine disorder that represents the most common cause of anovulatory infertility worldwide. Affecting approximately 8–13% of women of reproductive age globally, PCOS exerts far-reaching consequences on reproductive, metabolic, and psychological health [1, 33]. Despite decades of research, the precise etiology of PCOS remains incompletely understood, reflecting the syndrome's inherent

heterogeneity and the interplay of genetic, epigenetic, neuroendocrine, metabolic, and environmental factors [9, 32].

The Rotterdam Consensus criteria of 2003 define PCOS by the presence of at least two of the following three features: oligo-anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound—after the exclusion of other causes [22]. However, these diagnostic criteria remain a subject of debate because they capture a phenotypically diverse population in whom the underlying pathogenic drivers may differ substantially [1, 10]. This heterogeneity complicates both research and clinical management, as treatment strategies must be tailored to the individual patient's dominant phenotype and reproductive goals.

At its core, PCOS-related infertility arises primarily from chronic oligo-anovulation, which interrupts the ordered follicular development necessary for the release of a competent oocyte [7, 17]. The mechanisms underlying this anovulatory state are multifactorial, involving disordered hypothalamic-pituitary-ovarian (HPO) axis signaling, intrinsic ovarian dysfunction driven by hyperandrogenism and insulin resistance, systemic low-grade chronic inflammation, and disrupted intraovarian paracrine regulation [4, 19, 30]. Superimposed upon these pathophysiological processes are substantial genetic contributions, with genome-wide association studies (GWAS) identifying numerous susceptibility loci spanning genes involved in gonadotropin signaling, steroidogenesis, insulin action, and energy metabolism [9, 36].

This literature review provides a comprehensive synthesis of the current understanding of PCOS genetics, the interlocking pathogenic mechanisms that impair fertility, and the evidence-based therapeutic strategies for restoring ovulatory function and achieving successful pregnancy. By integrating insights from molecular biology, reproductive endocrinology, and clinical trial data, this review aims to offer a framework for understanding and managing this challenging condition.

2. Epidemiology and Diagnostic Considerations

The reported prevalence of PCOS varies widely—from 5% to 20%—largely because of differences in the diagnostic criteria applied and the populations studied [1, 33]. The three most widely used diagnostic frameworks are the NIH/NICHD criteria (1990), which require hyperandrogenism and oligo-anovulation; the broader Rotterdam criteria (2003), which add polycystic ovarian morphology as a defining feature; and the Androgen Excess Society (AES) criteria (2006), which emphasize hyperandrogenism as the central feature [22]. Each set of criteria yields a different prevalence estimate and a different patient population, underscoring the need for phenotypic characterization in clinical practice.

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Pitfalls in PCOS diagnosis are numerous. Polycystic ovarian morphology on ultrasound is a normal finding in up to 20–30% of healthy women, and serum androgen assays may lack the sensitivity and specificity required for accurate biochemical assessment of hyperandrogenism [22]. Anti-Müllerian hormone (AMH) has emerged as a promising surrogate marker of follicular pool size and PCOS severity, with markedly elevated levels reflecting the arrested follicular development characteristic of the syndrome [29]. Nonetheless, AMH thresholds for PCOS diagnosis are not yet universally standardized.

PCOS also exhibits significant comorbidity with other endocrine conditions. An association with subclinical hypothyroidism has been reported, with shared autoimmune and metabolic mechanisms potentially contributing to overlapping clinical presentations [27]. Sleep-disordered breathing, including obstructive sleep apnea, is more prevalent among women with PCOS than in the general population, driven by obesity, hyperandrogenism, and insulin resistance [31]. These comorbidities must be addressed in a comprehensive management plan.

3. Pathogenesis of PCOS-Related Infertility

3.1 Neuroendocrine Dysregulation and the HPO Axis

At the apex of PCOS pathogenesis lies dysregulation of the hypothalamic-pituitary-ovarian axis. Women with PCOS characteristically exhibit an accelerated GnRH pulse frequency, which preferentially stimulates pituitary LH synthesis and secretion while relatively suppressing FSH output [19, 28]. The resulting elevated LH-to-FSH ratio drives excessive ovarian androgen production by theca cells while simultaneously impairing the FSH-dependent granulosa cell maturation and aromatase activity necessary for estrogen synthesis and follicular development [4, 28].

The neuroendocrine origins of accelerated GnRH pulsatility in PCOS involve dysregulation of hypothalamic KNDy neurons and impaired progesterone-mediated negative feedback on the GnRH pulse generator [19]. This feedback resistance, potentially mediated by altered kisspeptin sensitivity, perpetuates the tonic state of LH hypersecretion even in the absence of ovulation and adequate luteal progesterone [19, 34]. Central adiposity and insulin resistance further contribute to HPO axis disruption by increasing bioavailable androgens and modulating hypothalamic insulin and leptin signaling, creating a self-reinforcing cycle of anovulation [19].

3.2 Hyperandrogenism: Mechanisms and Consequences

Hyperandrogenism is the cardinal biochemical feature of PCOS and a principal driver of the reproductive and metabolic complications of the syndrome [28]. Ovarian androgen excess arises primarily from intrinsic theca cell

hyperactivity—characterized by upregulated expression of the steroidogenic enzymes CYP17A1 and HSD3B2—compounded by LH-driven stimulation and, in some women, adrenal androgen excess [28, 32]. Reduced hepatic sex hormone-binding globulin (SHBG) production, consequent to hyperinsulinemia, amplifies the biological activity of circulating androgens by increasing the free androgen fraction [6].

Within the ovary, androgen excess profoundly disrupts follicular dynamics. Although low-to-moderate androgen concentrations enhance early antral follicle development by upregulating FSH receptor expression in granulosa cells, the chronic supraphysiological androgen milieu in PCOS impairs granulosa cell differentiation, promotes follicular arrest at the 5–8 mm stage, and contributes to the characteristic polycystic morphology [4, 18]. Recent evidence implicates ferroptosis—a form of regulated cell death driven by iron-dependent lipid peroxidation—as a mechanism by which androgen excess induces granulosa cell injury and oocyte quality impairment in PCOS [18].

At the systemic level, hyperandrogenism contributes to peripheral insulin resistance, dyslipidemia, endothelial dysfunction, and the chronic low-grade inflammatory state characteristic of PCOS, creating a vicious cycle in which metabolic dysfunction further amplifies androgen excess [6, 30].

3.3 Insulin Resistance and Compensatory Hyperinsulinemia

Insulin resistance affects approximately 50–70% of women with PCOS, irrespective of body mass index, and is now recognized as a core pathogenic feature rather than simply a consequence of obesity [38]. The mechanisms of insulin resistance in PCOS are multifactorial and tissue-specific. In skeletal muscle and adipose tissue, post-receptor defects in insulin signaling—including reduced IRS-1 phosphorylation, diminished PI3K/Akt pathway activation, and increased serine phosphorylation of the insulin receptor substrate—impair glucose uptake [38]. These defects coexist with preserved insulin sensitivity in ovarian theca cells, where hyperinsulinemia paradoxically stimulates androgen biosynthesis via upregulation of CYP17A1 and synergistic action with LH [6, 38].

Compensatory hyperinsulinemia further suppresses hepatic SHBG production, increases IGF-1 bioavailability, and augments LH-mediated theca cell androgen synthesis, thereby amplifying the hyperandrogenic state [6]. Insulin resistance also promotes dyslipidemia—characterized by elevated triglycerides, reduced HDL cholesterol, and increased small dense LDL particles—and contributes to the elevated cardiovascular disease risk associated with PCOS [6, 11]. At the cellular level, impaired mitochondrial oxidative phosphorylation and

increased reactive oxygen species generation in insulin-resistant tissues contribute to the systemic metabolic dysfunction [37].

Lipid metabolomic and proteomic analyses have revealed distinct lipid profiles in PCOS, including alterations in ceramides, lysophosphatidylcholines, and sphingomyelins, which may contribute to both insulin signaling impairment and inflammatory pathway activation [26]. These metabolomic signatures hold promise as future biomarkers for PCOS phenotyping and treatment monitoring.

3.4 Chronic Low-Grade Inflammation

Chronic low-grade inflammation is now well-established as a feature of PCOS, contributing to insulin resistance, hyperandrogenism, and ovulatory dysfunction through interconnected inflammatory pathways [8, 30]. Women with PCOS demonstrate elevated circulating concentrations of pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-18 (IL-18), tumor necrosis factor-alpha (TNF-alpha), and C-reactive protein (CRP), as well as increased monocyte activation and aberrant innate immune responses [12, 30].

The sources of chronic inflammation in PCOS are multiple. Adipose tissue dysfunction, particularly in visceral fat depots, generates a sustained pro-inflammatory cytokine milieu [30]. Hyperglycemia and lipotoxicity activate the NLRP3 inflammasome and nuclear factor-kappa B (NF-kB) signaling pathways in immune cells, perpetuating cytokine production [12]. Within the ovary itself, activated macrophages, altered natural killer cell activity, and dysregulated complement system components may impair the delicate immune environment necessary for folliculogenesis, oocyte maturation, and embryo implantation [14]. Immunological factors contributing to infertility include impaired endometrial receptivity, altered uterine natural killer cell function, and elevated anti-nuclear antibody titers observed in some PCOS patients [14].

3.5 Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction has emerged as a significant contributor to the pathophysiology of PCOS, linking metabolic impairment with reproductive failure [8, 37]. Mitochondria in granulosa cells, oocytes, and peripheral tissues of women with PCOS exhibit abnormalities in electron transport chain activity, impaired ATP synthesis, and increased generation of reactive oxygen species (ROS) [37]. Elevated ROS levels induce oxidative damage to cellular macromolecules, activate inflammatory signaling cascades, and impair insulin receptor function, creating a molecular nexus between metabolic dysfunction, inflammation, and ovarian pathology [8].

In oocytes and granulosa cells, mitochondrial dysfunction compromises the energy substrate availability necessary for meiotic maturation, fertilization, and

early embryo development, contributing to the reduced oocyte quality and embryo development rates observed in PCOS patients undergoing ART [37]. Oxidative stress also promotes apoptosis of granulosa cells and contributes to follicular atresia, reducing the pool of developmentally competent follicles [8].

3.6 Endoplasmic Reticulum Stress

Endoplasmic reticulum (ER) stress, triggered by the accumulation of misfolded proteins within the ER lumen, activates the unfolded protein response (UPR) and has been implicated in PCOS pathogenesis [15]. Hyperglycemia, lipotoxicity, and androgen excess—all features of PCOS—are potent inducers of ER stress in ovarian granulosa cells, theca cells, and hepatocytes [15]. Sustained UPR activation promotes cellular apoptosis through CHOP-dependent pathways and impairs insulin signaling via JNK-mediated serine phosphorylation of IRS-1, thereby contributing to insulin resistance [15]. In the ovary, ER stress-induced granulosa cell apoptosis may disrupt the paracrine support necessary for follicular maturation and oocyte competence.

3.7 Anti-Müllerian Hormone Dysregulation

Anti-Müllerian hormone (AMH) is produced by granulosa cells of small antral follicles and serves as a potent inhibitor of FSH-mediated follicular recruitment and aromatase activity [29]. In women with PCOS, circulating AMH concentrations are two- to four-fold higher than those in eumenorrheic controls, reflecting the dramatically increased number of small antral follicles arrested in early development [29]. This AMH excess reinforces follicular arrest by suppressing FSH action, impairing FSH receptor expression in granulosa cells, and reducing intraovarian estrogen production, thereby contributing to the anovulatory phenotype [29].

Emerging evidence suggests that elevated AMH may also exert central effects, modulating GnRH neuron activity and contributing to LH hypersecretion in PCOS [29]. The transgenerational transmission of PCOS through prenatal AMH exposure—demonstrated in experimental models—positions elevated AMH not merely as a consequence of follicular excess but potentially as a causal driver of the syndrome's propagation [23, 29].

3.8 Extracellular Matrix and Ovarian Microenvironment

The extracellular matrix (ECM) of the ovary provides structural and signaling support for folliculogenesis, and its dysregulation has been increasingly recognized in PCOS pathogenesis [20]. In PCOS ovaries, excessive collagen deposition, increased matrix metalloproteinase inhibitor activity, and dysregulated ECM remodeling create a fibrotic microenvironment that impedes normal follicular growth, ovulation, and corpus luteum formation [20]. This ovarian fibrosis is

driven by transforming growth factor-beta (TGF-beta) signaling, altered fibroblast activity, and the pro-inflammatory microenvironment characteristic of the syndrome [20]. Strategies targeting ECM remodeling are under investigation as potential therapeutic approaches to restore normal follicular dynamics.

4. Critical Appraisal of Diagnostic Methods

Despite decades of clinical use, the diagnostic frameworks applied to polycystic ovary syndrome remain substantially flawed, yielding inconsistent patient populations across studies and clinical settings. The absence of a single pathognomonic biomarker or universally accepted gold standard means that PCOS diagnosis is inherently inferential — a process of exclusion and pattern recognition rather than confirmed biological identification. This section critically examines the principal methodological weaknesses of current diagnostic approaches, including the contested criteria systems, the limitations of biochemical androgen assessment, the ambiguities surrounding ultrasound-based ovarian morphology, and the inadequacy of existing frameworks in capturing the syndrome's full phenotypic and demographic diversity.

4.1 The Multiplicity and Inconsistency of Diagnostic Criteria

The coexistence of three competing diagnostic frameworks — the NIH/NICHD criteria (1990), the Rotterdam criteria (2003), and the Androgen Excess Society criteria (2006) — is perhaps the most fundamental structural flaw in PCOS diagnosis. Each system operationalises the syndrome differently, yielding estimated prevalence figures that range from 5% to 20% in the same general population. Because the Rotterdam criteria are the broadest, permitting diagnosis on the basis of any two of three features (oligo-anovulation, hyperandrogenism, or polycystic ovarian morphology), they enrol a substantially larger and more phenotypically diverse group than the narrower NIH criteria, which mandate both hyperandrogenism and oligo-anovulation. This means that a woman classified as having PCOS under Rotterdam may not meet NIH criteria at all, and vice versa. The practical consequence is that findings from studies conducted under different criteria are not directly comparable, undermining the reproducibility of the evidence base and complicating meta-analytic synthesis. Until a single, internationally ratified criterion is adopted, the field will remain burdened by definitional inconsistency that limits both basic research and clinical translation.

4.2 Unreliability of Biochemical Androgen Assessment

Biochemical hyperandrogenism is considered a cornerstone feature of PCOS, yet its reliable measurement in clinical practice is notoriously difficult. Most routine immunoassay-based testosterone assays lack the sensitivity and specificity required for accurate detection of the modest androgen elevations characteristic of PCOS in

women, particularly at the lower end of the abnormal range. Liquid chromatography–tandem mass spectrometry (LC-MS/MS) is the reference standard for androgen quantification but remains unavailable in many clinical laboratories and is rarely used in routine practice. Furthermore, there is no consensus on which androgen fractions should be measured: total testosterone, free testosterone, free androgen index, and androstenedione all have different sensitivities for detecting hyperandrogenism, and laboratories apply different reference ranges derived from populations of varying characteristics. The biological variability of androgen levels — fluctuating across the menstrual cycle, with body weight, and with age — adds additional noise. The result is that a substantial proportion of women with clinically apparent hyperandrogenism (e.g., hirsutism, acne) will have "normal" laboratory values depending on the assay and threshold used, whilst some women without clinical signs will be flagged biochemically. This unreliability inevitably produces both over-diagnosis and under-diagnosis, particularly in lean or adolescent populations.

4.3 Ambiguity of Ultrasound-Based Polycystic Ovarian Morphology

The use of pelvic ultrasound to identify polycystic ovarian morphology (PCOM) is a further source of diagnostic error. As noted in Section 2, PCOM is observed in 20–30% of healthy, eumenorrheic women with no other features of PCOS, meaning that its presence as an isolated finding carries low specificity. The threshold for defining PCOM has shifted significantly with the advent of high-resolution transvaginal transducers: the original Rotterdam criterion of 12 or more follicles per ovary in a single plane has been superseded in many guidelines by a threshold of 20 or more follicles, reflecting improved imaging resolution rather than a biological reclassification. This threshold creep generates substantial inconsistency across studies and clinical contexts, as many older datasets and lower-resource settings continue to apply the 12-follicle criterion. Additionally, ultrasound-based follicle counting is operator-dependent, with significant inter-observer variability reported even among experienced sonographers. The inability to standardise transducer frequency, imaging planes, and follicle measurement protocols across institutions means that PCOM as a diagnostic variable is neither reproducible nor universally comparable — a critical de

4.4 The Limitations of AMH as a Diagnostic Surrogate

Anti-Müllerian hormone has attracted considerable interest as an objective, quantitative surrogate for both PCOM and overall PCOS severity, with markedly elevated serum concentrations reflecting the expanded pool of small antral follicles. However, several methodological limitations restrict its diagnostic utility. First, AMH assays differ substantially between manufacturers in their calibration

standards, antibody targets, and reported normal ranges, rendering cross-laboratory comparisons unreliable. Second, AMH levels are physiologically influenced by age, ethnicity, BMI, hormonal contraceptive use, and seasonal variation — none of which are consistently accounted for in published diagnostic cut-offs. Third, AMH thresholds proposed for PCOS diagnosis vary widely across studies (typically ranging from 3.4 to 5.0 ng/mL), and no universally standardised threshold has been endorsed by major professional societies. The 2023 international PCOS evidence-based guidelines explicitly acknowledge that AMH cannot replace ultrasound as a diagnostic criterion pending further standardisation. Thus, while AMH holds genuine promise as a complementary biomarker, its premature adoption as a primary diagnostic tool risks introducing a new source of diagnostic inconsistency to replace the one it was meant to resolve.

4.5 Diagnostic Challenges in Adolescents and Ethnic Minorities

Existing diagnostic criteria were developed and validated predominantly in adult White European populations, creating significant generalisability problems. In adolescents, irregular menstrual cycles and multi-follicular ovarian morphology are physiologically normal in the first two to three years following menarche, meaning that standard criteria systematically over-diagnose PCOS in this age group. Current guidelines recommend deferring formal diagnosis until two years post-menarche and requiring all three Rotterdam features to be present simultaneously — yet many clinicians continue to apply adult criteria to adolescent patients, with potential harms including unnecessary pharmacological treatment, adverse labelling effects, and iatrogenic anxiety. In ethnic minority populations, the diagnostic picture is further complicated by documented differences in the phenotypic expression of PCOS: South Asian women are more likely to present with pronounced insulin resistance and metabolic comorbidity at lower BMI thresholds, while East Asian women exhibit a higher prevalence of lean PCOS with less overt hirsutism. The Ferriman–Gallwey scoring system used to assess hirsutism was calibrated on largely White populations and is known to underestimate clinically meaningful hair growth in some ethnic groups whilst potentially overcounting in others. These demographic gaps in the diagnostic evidence base mean that a clinically significant proportion of PCOS cases are misclassified or delayed in diagnosis, with downstream consequences for fertility outcomes and long-term metabolic health.

5. Management of PCOS-Related Infertility

5.1 Lifestyle Modification and Weight Management

For overweight and obese women with PCOS-related infertility, lifestyle intervention—comprising caloric restriction, increased physical activity, and

behavioral modification—represents the cornerstone of first-line management [1, 33]. Even modest weight loss of 5–10% of body weight has been shown to reduce circulating androgen and insulin concentrations, restore spontaneous menstrual cyclicity and ovulation, and improve pregnancy rates without pharmacological intervention [11, 33]. Weight reduction improves the hormonal milieu by increasing hepatic SHBG production, reducing LH pulse frequency, decreasing adipokine-driven inflammation, and enhancing insulin receptor sensitivity in peripheral tissues [11].

The composition of the dietary intervention may also matter. Low glycemic index diets and Mediterranean-style dietary patterns have demonstrated particular benefit in improving insulin sensitivity and reducing inflammatory markers in PCOS [33]. High-intensity interval training has shown advantages over continuous moderate-intensity exercise for improving insulin sensitivity and androgenic profiles in PCOS [33]. Regardless of the specific modality, lifestyle intervention should be recommended as the initial therapeutic approach for all overweight or obese PCOS patients seeking fertility treatment, given its favorable risk-benefit profile.

5.2 Ovulation Induction: First- and Second-Line Agents

For women with PCOS who fail to conceive with lifestyle modification alone, pharmacological ovulation induction is indicated [7, 24]. Historically, clomiphene citrate (CC), a selective estrogen receptor modulator, was the first-line agent for ovulation induction in PCOS, with ovulation rates of 60–85% and cumulative pregnancy rates of 30–40% over multiple treatment cycles [24]. However, CC's antiestrogenic effects on the endometrium and cervical mucus may impair implantation, and up to 15–25% of patients exhibit CC-resistance, defined by failure to ovulate despite maximal doses [7].

Letrozole, a third-generation aromatase inhibitor, has emerged as the preferred first-line ovulation induction agent in PCOS following the landmark PPCOS II trial, which demonstrated significantly higher live birth rates with letrozole compared to clomiphene citrate in anovulatory PCOS [5, 17]. By inhibiting peripheral and ovarian estrogen biosynthesis, letrozole removes the negative estrogen feedback on the hypothalamus, stimulating a physiological rise in FSH secretion and monofollicular development, with lower rates of multiple gestation than exogenous gonadotropin therapy [5, 17]. Letrozole also lacks the antiestrogenic endometrial effects of clomiphene, potentially enhancing implantation rates [17].

Metformin, a biguanide insulin-sensitizing agent, may be used in conjunction with ovulation induction agents in insulin-resistant or obese PCOS patients [2]. By

reducing hepatic gluconeogenesis and improving peripheral insulin sensitivity, metformin lowers circulating insulin and androgen concentrations, restores menstrual regularity, and improves ovulatory responses to clomiphene citrate [2]. Metformin monotherapy is less effective than letrozole for ovulation induction but may have a role in preventing ovarian hyperstimulation syndrome (OHSS) in high-responder patients and as an adjunct in ART cycles [2, 25].

5.3 Gonadotropin Therapy

For women who fail to ovulate or conceive with oral ovulation induction agents, low-dose step-up gonadotropin protocols represent the standard second-line approach [7, 25]. Exogenous FSH administration using a low-dose step-up regimen—beginning at 37.5–75 IU/day and increasing incrementally every 7–14 days based on ultrasound follicular monitoring—aims to identify the FSH threshold necessary for dominant follicle selection while minimizing the risk of multifollicular development and OHSS [7, 25]. Cycle fecundity rates with gonadotropin ovulation induction in PCOS are comparable to those of letrozole, but the requirements for intensive monitoring and the risks of multiple pregnancy and OHSS necessitate careful patient selection and close surveillance [7].

5.4 Laparoscopic Ovarian Surgery

Laparoscopic ovarian drilling (LOD) is a surgical ovulation induction method in which multiple punctures are made in the ovarian cortex using electrosurgery or laser energy, reducing the androgen-producing theca cell mass and transiently restoring HPO axis sensitivity to negative feedback [17, 25]. LOD is associated with ovulation and pregnancy rates comparable to gonadotropin therapy in CC-resistant PCOS, with the advantage of a reduced multiple pregnancy risk and the potential for sustained improvement in ovulatory function over several years [17]. However, the potential for postoperative periovarian adhesion formation, which may compromise subsequent fertility, and the need for general anesthesia have tempered enthusiasm for this approach, and LOD is generally reserved for women requiring laparoscopy for other indications or those in whom gonadotropin monitoring is impractical [7, 25].

5.5 GLP-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists, including liraglutide, semaglutide, and exenatide, have attracted increasing interest as adjunctive treatments for PCOS in obese and insulin-resistant patients [3]. Beyond their potent weight-reduction effects, GLP-1 receptor agonists improve insulin sensitivity, reduce circulating androgen concentrations, decrease inflammatory cytokine levels, and may restore menstrual regularity and ovulatory function in women with PCOS [3]. Preliminary clinical data suggest that GLP-1 receptor agonists may enhance the

efficacy of ovulation induction agents and improve metabolic parameters in a manner complementary to, and in some cases superior to, metformin [3]. While randomized controlled trial data specifically addressing fertility outcomes in PCOS are still accumulating, GLP-1 receptor agonists represent a promising emerging therapeutic option, particularly for women with significant obesity and metabolic comorbidity [3].

5.6 Assisted Reproductive Technologies in PCOS

In vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI) is the definitive treatment for PCOS-related infertility refractory to first- and second-line ovulation induction, or when additional infertility factors such as tubal disease or male factor infertility are present [16, 25]. Women with PCOS face specific challenges in IVF, including a high risk of OHSS consequent to their large antral follicle count and exaggerated follicular response to gonadotropin stimulation, high dropout rates due to cycle cancellation, and variable oocyte quality [16].

Contemporary IVF protocols for PCOS patients have been significantly refined to mitigate OHSS risk. The GnRH antagonist stimulation protocol—which allows GnRH agonist triggering of final oocyte maturation instead of hCG—has become the standard of care in PCOS patients undergoing IVF because it virtually eliminates the risk of severe late-onset OHSS [16, 25]. Freeze-all strategies, in which all embryos are cryopreserved and transferred in a subsequent natural or programmed frozen embryo transfer cycle, further reduce OHSS risk and may improve endometrial receptivity by avoiding the supraphysiological hormonal milieu of the stimulation cycle [16, 25].

Metformin pretreatment is recommended in PCOS patients undergoing IVF to reduce OHSS incidence, improve oocyte quality, and enhance embryo development [2, 16]. Individualized gonadotropin dosing based on antral follicle count and AMH levels, along with frequent ultrasound and estradiol monitoring, is essential to optimize the stimulation response while minimizing the risk of cycle cancellation and adverse outcomes [16]. Emerging evidence supports the use of in vitro maturation (IVM) of immature oocytes retrieved from unstimulated or minimally stimulated PCOS ovaries as a strategy to avoid OHSS entirely, with improving clinical pregnancy and live birth rates as laboratory techniques advance [16].

6. Conclusion

Polycystic ovary syndrome represents a paradigmatic complex disorder whose heterogeneous clinical manifestations arise from the convergence of multiple genetic, epigenetic, neuroendocrine, metabolic, and environmental factors. This literature review has synthesized current evidence demonstrating that PCOS-related infertility emerges from a constellation of interacting pathogenic processes:

a polygenic susceptibility architecture involving genes in gonadotropin signaling, steroidogenesis, and insulin action; epigenetic programming and potential transgenerational transmission; neuroendocrine dysregulation characterized by GnRH pulse generator acceleration and LH hypersecretion; intrinsic ovarian hyperandrogenism with disrupted folliculogenesis; systemic and intraovarian insulin resistance with compensatory hyperinsulinemia; chronic low-grade inflammation and immune dysregulation; mitochondrial dysfunction and oxidative stress; ER stress-mediated cellular injury; AMH-driven follicular arrest; and ECM dysregulation creating an inhospitable ovarian microenvironment.

The management of PCOS-related infertility requires a stepwise, individualized approach that begins with lifestyle intervention and progresses through oral ovulation induction with letrozole as the preferred first-line agent, adjunctive insulin sensitization with metformin or GLP-1 receptor agonists, gonadotropin therapy, and ultimately ART with OHSS-prevention strategies including GnRH antagonist protocols and freeze-all policies. Emerging therapeutic approaches targeting the molecular underpinnings of PCOS—including novel androgen receptor modulators, anti-inflammatory agents, mitochondria-targeted therapies, and epigenetic modulators—hold promise for improving outcomes in this complex patient population.

Given the complexity and lifelong health consequences of PCOS, a multidisciplinary approach involving reproductive endocrinologists, metabolic physicians, nutritionists, and mental health professionals is essential. Future research should prioritize elucidating the causal relationships between genetic variants and phenotypic subtypes, developing validated biomarkers for phenotypic classification and treatment response prediction, and conducting large randomized controlled trials of emerging pharmacological agents. By advancing the mechanistic understanding of PCOS, the field can move toward precision medicine approaches that match targeted therapies to specific disease subtypes, ultimately improving reproductive and long-term health outcomes for the millions of women affected by this condition worldwide.

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