REVIEW

Polycystic ovary syndrome and infertility: A narrative review of diagnostic and therapeutic approaches

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Objective: To synthesize current evidence on mechanisms, diagnostic evaluation, and treatment of infertility in PCOS, with emphasis on phenotype-specific implications and integrative management.

Methods: A narrative review was conducted using PubMed, Scopus, and Web of Science from January 2015 to March 2024. Search terms included "PCOS," "infertility," "phenotype," "letrozole," "metformin," "gonadotropins," and "ART." Eligible studies involved human females aged 18–45 years, written in English, and focused on PCOS-related infertility. Randomized trials, meta-analyses, and international guidelines were critically assessed for methodological rigor and clinical relevance.

Results: PCOS accounts for 70–80% of anovulatory infertility, with marked variability across phenotypes. Phenotype A, combining hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, carries the greatest reproductive and metabolic burden. Biomarkers such as AMH, testosterone, DHEAS, fasting insulin, and HOMA-IR improve risk stratification. Lifestyle modification restores ovulation in up to 60% of overweight patients. Letrozole is superior to clomiphene, while gonadotropins and ART are effective in resistant cases. Metformin enhances ovulatory and pregnancy outcomes in insulin-resistant women. IVF protocols using antagonists and agonist triggers improve safety by reducing ovarian hyperstimulation syndrome. Psychological comorbidities, particularly anxiety and depression, are frequent and negatively affect fertility outcomes.

Conclusion: PCOS-related infertility requires a personalized, multidisciplinary approach. Integration of phenotype-based assessment, biomarker evaluation, lifestyle intervention, and tailored reproductive strategies optimizes outcomes. Addressing metabolic and psychological dimensions further improves reproductive success and long-term health.

Keywords: polycystic ovary syndrome, infertility, letrozole, lifestyle modification, ART

Introduction

Polycystic ovary syndrome (PCOS) represents a multifactorial endocrine disorder with significant clinical heterogeneity, affecting an estimated 8% to 13% of reproductive-aged women, depending on the diagnostic standards applied [1]. As the leading endocrine cause of chronic anovulation, PCOS is frequently implicated in infertility, while also being associated with a wide constellation of reproductive, metabolic, and psychological alterations [2].

Over time, the definition of PCOS has undergone considerable refinement. The most widely endorsed diagnostic model remains the 2003 Rotterdam criteria, which stipulate the presence of at least two out of three defining features: oligo- or anovulatory cycles, hyperandrogenism (either clinical or biochemical), and polycystic ovarian morphology identified on ultrasonography [3]. Although this framework expanded diagnostic inclusivity, it also introduced challenges in terms of phenotypic classification and variability in prevalence estimations across populations [4].

Based on the Rotterdam criteria, four distinct phenotypes of PCOS have been described: (a) phenotype A, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology; (b) phenotype B, defined by hyperandrogenism and ovulatory dysfunction in the absence of polycystic ovarian morphology; (c) phenotype C, which includes hyperandrogenism and polycystic ovarian morphology but with preserved ovulation; and (d) phenotype D, marked by ovulatory dysfunction and polycystic ovarian morphology without hyperandrogenism. These phenotypic variants differ in terms of reproductive, metabolic, and psychological implications, with phenotype A generally considered the most severe due to its association with increased metabolic and reproductive risk [1,3,9].

The etiopathogenesis of PCOS integrates numerous interacting mechanisms, including hereditary susceptibility, dysregulation of the hypothalamic-pituitary-ovarian axis, systemic insulin resistance, androgen excess, and a pro-inflammatory milieu [5]. One key hormonal aberration involves increased luteinizing hormone (LH) secretion relative to follicle-stimulating hormone (FSH), contributing to disrupted folliculogenesis and persistent anovulation [6]. Concurrently, hyperinsulinemia amplifies ovarian androgen synthesis and suppresses sex hormone-binding globulin (SHBG) production, thereby enhancing circulating free androgen levels [7]. The cumulative effect of these hormonal imbalances is impaired follicle maturation and compromised oocyte quality [8].

From a reproductive perspective, PCOS often presents with irregular menstrual cycles, ovulatory dysfunction,

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reduced fecundity, and a heightened risk for early pregnancy loss and obstetric complications [9]. The syndrome is further complicated by frequent overlap with metabolic syndrome features such as visceral adiposity, atherogenic dyslipidemia, insulin resistance, and elevated blood pressure—factors that may exacerbate infertility [10].

In recent years, attention has also shifted toward the psychological burden of PCOS. Affected women commonly experience reduced quality of life, mood disturbances, heightened anxiety, depressive symptoms, and body image dissatisfaction, particularly in relation to hirsutism and weight gain [11]. These emotional challenges may negatively impact motivation, treatment compliance, and fertility outcomes [12].

Considering the complexity and multifaceted expression of PCOS, its management must adopt a personalized and interdisciplinary strategy. The objective of this review is to synthesize current evidence on the pathophysiological mechanisms, diagnostic evaluation, and therapeutic approaches related to infertility in women with PCOS, while highlighting clinically relevant trends and unmet needs in reproductive care [13].

Materials and methods

This narrative review was conducted using a structured, evidence-based approach in accordance with established methodologies for scoping and narrative syntheses [14]. A comprehensive literature search was carried out across three major biomedical databases—PubMed, Scopus, and Web of Science—covering the period from January 2015 to March 2024 [15]. These databases were specifically selected because they are widely recognized as the most comprehensive and reliable biomedical sources, covering both clinical and basic research. PubMed ensures extensive indexing of peer-reviewed medical literature, Scopus provides multidisciplinary coverage and citation tracking, while Web of Science offers high-quality records with robust cross-referencing. Together, they minimize redundancy and maximize the likelihood of capturing all relevant studies.

The search strategy included combinations of Medical Subject Headings (MeSH) and keywords such as "polycystic ovary syndrome," "PCOS," "infertility," "anovulation," "letrozole," "clomiphene citrate," "gonadotropins," "metformin," and "assisted reproduction," utilizing Boolean operators to improve precision and relevance [15].

Studies were included if they met all of the following criteria: (1) published in peer-reviewed journals, (2) written in English, (3) conducted on human female participants aged 18 to 45, and (4) focused on the relationship between PCOS and infertility, either from a diagnostic, pathophysiological, or therapeutic standpoint [16]. Exclusion criteria were: case reports, conference abstracts, editorial letters, animal or in vitro studies, and studies lacking full-text access or methodological rigor [16].

From an initial pool of 402 articles, duplicates were removed, and titles and abstracts were screened for eligibility. A total of 112 full-text articles were evaluated, and 40 studies were ultimately included based on their clinical relevance and methodological strength [17]. The selection process adhered to the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) framework [17].

Each included study was independently assessed by two reviewers using validated critical appraisal tools appropriate to study type. For randomized controlled trials, the Cochrane Risk of Bias tool was employed, while systematic reviews were evaluated using the AMSTAR 2 checklist [18,19]. Data were extracted regarding study design, sample size, participant characteristics (e.g., age, body mass index, PCOS phenotype), and fertility-related outcomes such as ovulation, conception, and pregnancy rates [19].

Additionally, key clinical guidelines and consensus documents from internationally recognized medical societies—including the European Society of Human Reproduction and Embryology (ESHRE), the American Society for Reproductive Medicine (ASRM), and the Endocrine Society—were reviewed to ensure alignment with current clinical practice standards [20].

The evidence was organized thematically into five core domains relevant to PCOS-related infertility: (1) pathophysiological mechanisms, (2) diagnostic evaluation, (3) epidemiological prevalence, (4) therapeutic interventions, and (5) assisted reproductive technologies [21]. Reference management was performed using the Vancouver citation style, ensuring consistent numerical order and accurate bibliographic correlation throughout the manuscript [22].

The study selection process is illustrated in a PRISMA-adapted flowchart (Figure 1), summarizing article identification, screening, inclusion, and exclusion steps [23]. The flowchart was constructed in accordance with PRISMA-ScR recommendations, and references for methodological guidance have been included [17,23].

Results

A total of 40 studies were included in this review, selected from an initial pool of 402 articles after duplicate removal and screening for relevance and methodological quality (Figure 1) [24]. Risk of bias was assessed separately for each study type using standardized instruments, including the Cochrane Risk of Bias tool for randomized trials and AMSTAR 2 for systematic reviews [25].

Pathophysiological mechanisms underlying infertility in PCOS

The primary contributor to infertility in PCOS is chronic anovulation resulting from dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis [26]. Elevated luteinizing hormone (LH) levels relative to follicle-stimulating hormone (FSH) impair follicular recruitment and lead to arrested folliculogenesis [27].
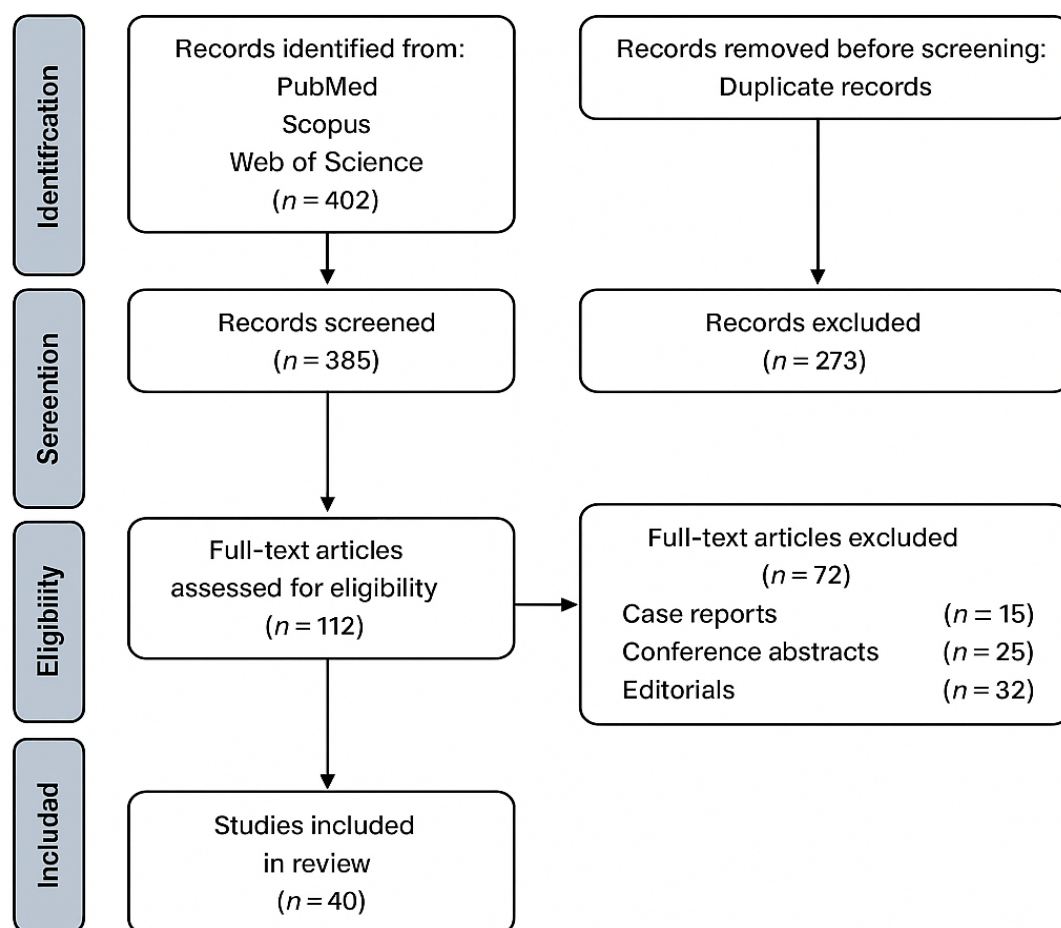
Fig. 1. PRISMA-adapted flow diagram for study selection. The flow diagram summarizes the selection process, including records identified, screened, excluded, and included, following PRISMA-ScR guidelines [17,23].

Hyperandrogenemia disrupts granulosa cell proliferation and differentiation, contributing to follicular atresia [28]. In over half of affected patients, insulin resistance further exacerbates androgen production by stimulating theca cells and reducing sex hormone-binding globulin (SHBG), **thus raising circulating free androgens** [29]. Chronic low-grade inflammation, frequently observed in PCOS **has also been shown to impair** oocyte competence and endometrial receptivity, thereby reducing implantation potential [30].

Prevalence and phenotypic variation of infertility in PCOS

PCOS accounts for approximately 70–80% of cases of anovulatory infertility [2]. Among women with PCOS, 40% to 60% report difficulty achieving pregnancy [31]. The distribution of infertility risk varies significantly across PCOS phenotypes [9].

Phenotype A (hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology) has the highest reproductive and metabolic burden, being associated with insulin resistance and obesity in a large proportion of patients [20]. Phenotype B (hyperandrogenism and ovulatory dysfunction without polycystic ovarian morphology) also carries significant infertility risk [21]. Phenotype C (hyperandrogenism with polycystic morphology but preserved ovulation) shows milder reproductive compromise [9]. Phenotype D (ovulatory dysfunction with polycystic morphology but no hyperandrogenism) is often associated with less severe metabolic features and comparatively better fertility outcomes [20].

The likelihood of infertility is particularly high in phenotypes that combine hyperandrogenism and obesity, where metabolic dysfunction further impairs reproductive potential [32].

Figure 2 illustrates the relative prevalence of phenotypes A–D among women with PCOS-related infertility, based on the Rotterdam criteria [9]. Phenotype A is generally the most frequent, followed by phenotypes C, D, and B, with distribution varying by study population [20,21].

Diagnostic biomarkers and imaging in the infertility workup

Anti-Müllerian hormone (AMH) levels are consistently elevated in women with PCOS, often exceeding 4.5 ng/mL, reflecting increased antral follicle count [33]. AMH serves as a predictor of ovarian response to stimulation and identifies patients at risk of ovarian hyperstimulation syndrome (OHSS) in assisted reproduction [34]. Transvaginal ultrasound remains essential in identifying polycystic ovarian morphology, defined by ≥20 follicles per ovary and/or ovarian volume >10 mL [35]. Although an LH/FSH
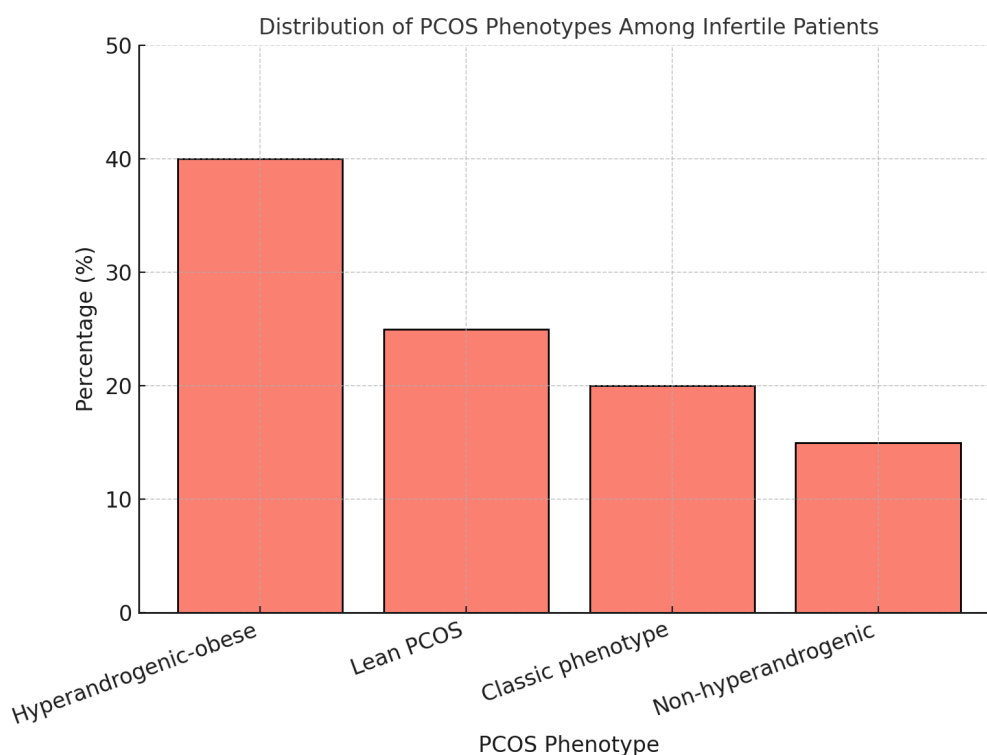
Fig. 2. Distribution of PCOS phenotypes among infertile patients.

ratio >2 is often observed, its diagnostic value is limited and should not be used in isolation [36].

Additional laboratory assessments provide a more comprehensive evaluation. Measurement of total and free testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione helps quantify hyperandrogenemia [28]. Fasting insulin and HOMA-IR are used to evaluate insulin resistance [31]. Lipid profile and glucose tolerance testing further identify metabolic risk factors that may exacerbate infertility [32].

Ovulation induction and treatment responsiveness
Lifestyle modification represents the cornerstone of initial management. Weight reduction through dietary interventions and structured physical activity can restore ovulation in 30–60% of overweight or obese PCOS patients [4]. Even modest reductions of 5–10% of body weight improve menstrual regularity and conception rates [31,32]. Beyond reproductive benefits, lifestyle interventions improve insulin sensitivity, reduce circulating androgens, and lower cardiometabolic risk, thereby enhancing long-term health outcomes [32].

Letrozole, an aromatase inhibitor, has emerged as the first-line pharmacological agent for ovulation induction, demonstrating superior ovulation and live birth rates compared to clomiphene citrate [5]. In a pivotal randomized trial, Legro et al. reported a live birth rate of 27.5% with letrozole versus 19.1% with clomiphene citrate [29]. Clomiphene citrate remains useful in selected patients, particularly those with normal BMI [30]. Its limitations include endometrial thinning and an increased risk of multiple gestations [6]. In women unresponsive to oral agents,

gonadotropin therapy can be considered, with careful monitoring due to the risk of multifollicular development and OHSS [6].

Figure 3 presents pooled data from randomized trials showing superior ovulation and live birth rates with letrozole compared to clomiphene citrate [5,29].

Role of insulin sensitizers in ovulation and pregnancy outcomes
Metformin improves ovulatory function in insulin-resistant PCOS patients [31]. Its benefits are particularly evident when combined with lifestyle measures [37]. Metformin has also been shown to reduce early pregnancy loss [37]. It may enhance clomiphene responsiveness in resistant cases [37]. While combining metformin with letrozole may yield additive benefits, current evidence remains inconclusive [38].

Assisted reproductive technologies in PCOS
When ovulation induction fails or additional infertility factors are present, in vitro fertilization (IVF) becomes the next therapeutic step [32]. PCOS patients present unique challenges in IVF cycles, including increased risk of OHSS [33]. This risk is particularly pronounced in patients with elevated AMH or antral follicle counts [33]. To reduce this risk, antagonist protocols using GnRH agonist triggers are preferred [39]. These strategies have demonstrated comparable pregnancy rates with improved safety profiles [39].

Figure 4 summarizes differences in clinical pregnancy and live birth outcomes between women with and without PCOS undergoing IVF, highlighting the elevated risk
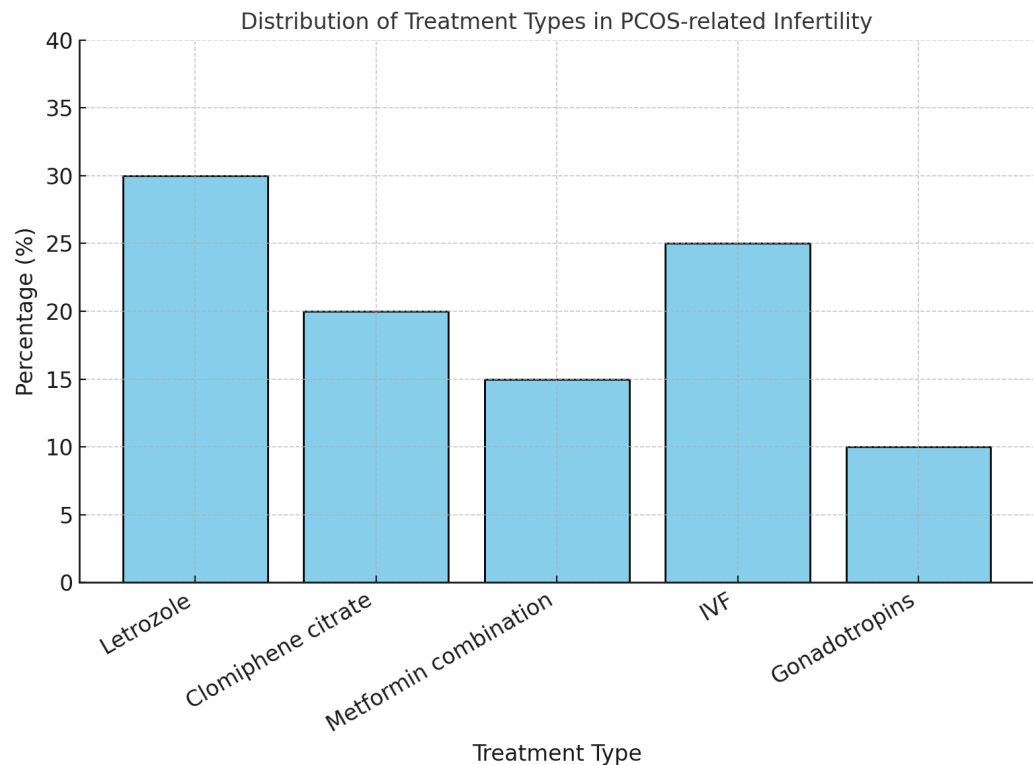
Fig. 3. Comparison of ovulation rates with letrozole versus clomiphene citrate.

of ovarian hyperstimulation syndrome in PCOS patients [32,33,39].

Discussion

Polycystic ovary syndrome (PCOS) presents as a heterogeneous clinical entity, necessitating a nuanced and phenotype-tailored approach to infertility management [1]. While the central pathophysiological features—namely ovulatory dysfunction, androgen excess, and insulin resistance—are well established, variations in clinical phenotype significantly impact both prognosis and treatment efficacy [3]. For instance, women with the so-called "metabolic
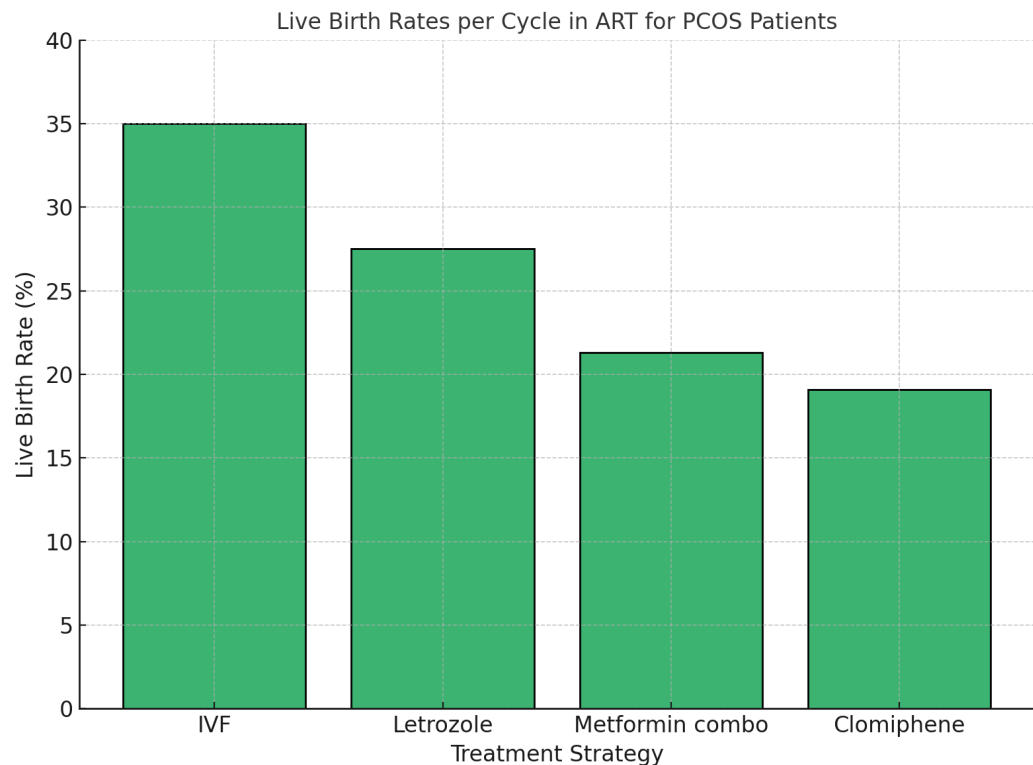

Fig. 4. IVF success rates in PCOS versus non-PCOS populations.

phenotype" (characterized by hyperandrogenism, obesity, and insulin resistance) tend to have a less favorable response to standard ovulation induction protocols compared to lean PCOS individuals [11].

Lifestyle modification remains the cornerstone of initial therapy in overweight or obese patients with PCOS, with proven benefits in improving menstrual cyclicity, insulin metabolism, and systemic inflammatory markers [4]. Evidence suggests that even modest weight reduction—between 5% and 10% of initial body weight—can restore spontaneous ovulation in a substantial proportion of cases [4]. Nevertheless, maintaining adherence to behavioral interventions is challenging, and many patients ultimately require adjunctive pharmacologic support [36].

Letrozole has emerged as the agent of choice for ovulation induction in PCOS, surpassing clomiphene citrate in terms of ovulatory and live birth outcomes [5]. Its mechanism, as an aromatase inhibitor, is associated with superior endometrial profiles and fewer antiestrogenic side effects, offering advantages in endometrial receptivity and pregnancy potential [29]. Clomiphene citrate continues to play a role in selected patients, especially those without significant metabolic impairment, though concerns persist regarding endometrial thinning and increased risk of multifetal pregnancies [25].

For individuals unresponsive to oral agents such as letrozole or clomiphene, gonadotropin-based therapies are a logical next step [6]. These treatments, however, necessitate close monitoring with transvaginal ultrasonography and serum estradiol measurements to mitigate the risk of ovarian hyperstimulation syndrome (OHSS) and multifollicular development [6]. Incremental dosing strategies, including low-dose step-up and step-down protocols, have been shown to enhance safety while maintaining effectiveness [27].

In women with insulin resistance, metformin serves as a valuable adjunct, particularly when combined with letrozole or clomiphene in patients with suboptimal ovulatory response [31]. Beyond its insulin-sensitizing action, metformin may confer benefits in reducing miscarriage rates and modulating androgen levels [37]. However, its efficacy as monotherapy in restoring ovulation is inconsistent, underscoring the need for appropriate patient selection [31].

When ovulation induction fails or other contributing factors such as tubal pathology or severe male infertility are present, assisted reproductive technologies—particularly in vitro fertilization (IVF)—become necessary [32]. Patients with PCOS undergoing IVF present unique challenges, most notably an elevated risk of OHSS due to high follicular sensitivity and elevated AMH or antral follicle counts [33]. To address this, GnRH antagonist protocols, coupled with agonist triggers and "freeze-all" embryo strategies, have become standard in high-responder PCOS populations [39].

Recent research efforts are directed toward optimizing ovarian stimulation protocols based on individualized markers, including AMH levels and AFC, to reduce risks and improve reproductive outcomes [34,35]. There is also increasing interest in the use of novel therapeutic agents, such as inositols and GLP-1 receptor agonists, for metabolic modulation in selected subgroups of PCOS patients [38]. Moreover, future advances may include pharmacogenomics-guided ovulation induction and refined prediction tools for ART-related complications [2].

Importantly, fertility treatment in PCOS should not focus exclusively on endocrine and reproductive endpoints [7]. The high prevalence of psychological comorbidities—particularly anxiety and depression—necessitates the integration of mental health support within fertility care [7]. Multidisciplinary collaboration, engaging gynecologists, endocrinologists, dietitians, and mental health professionals, is critical for achieving both successful conception and sustained improvement in patient quality of life [36].

This narrative review is limited by the heterogeneity of included studies, particularly in diagnostic criteria and outcome measures [24]. The absence of quantitative meta-analysis restricts the ability to perform comparative effect size analysis [17]. Despite these limitations, the thematic synthesis allows for clinically relevant interpretation of current evidence and provides practical guidance for fertility management in PCOS [25].

The original contribution of this review lies in its integrative perspective, which brings together pathophysiological mechanisms, phenotypic classification, laboratory biomarkers, lifestyle interventions, and reproductive technologies into a single comprehensive framework [40].

By emphasizing phenotypic variability, this review highlights clinically relevant differences that guide individualized therapeutic strategies, an approach often overlooked in conventional summaries [12].

In addition, the detailed analysis of laboratory assessments such as testosterone, DHEAS, fasting insulin, and HOMA-IR provides clinicians with practical tools for infertility risk stratification, complementing standard diagnostic criteria [41].

Another distinctive contribution is the prioritization of lifestyle modification as a therapeutic intervention, positioning it as a primary strategy with proven reproductive and metabolic benefits rather than as an adjunct [4].

Finally, by integrating guideline-based recommendations with recent trial evidence, this review offers a bridge between research and clinical practice, supporting evidence-informed decision-making in the management of infertility among PCOS patients [2].

Conclusion

Polycystic ovary syndrome (PCOS) continues to be recognized as the leading endocrine disorder affecting reproductive-aged women, exerting a substantial impact not only on fertility but also on long-term metabolic and psychosocial health [1]. The core contributors to infertility in PCOS (namely ovulatory dysfunction, androgen excess, insulin

resistance, and systemic inflammation) are increasingly well understood [3]. Nevertheless, their expression across clinical phenotypes remains heterogeneous, necessitating tailored treatment strategies [12].

Among pharmacologic options, letrozole has demonstrated superior efficacy over clomiphene citrate, particularly in cases involving metabolic dysfunction or previous failure of ovulation induction [5]. Metformin remains a valuable adjunct in the management of insulin resistance and ovulatory dysfunction [31]. While its efficacy as monotherapy is limited, when combined with letrozole or clomiphene it may enhance treatment outcomes and reduce the likelihood of early pregnancy loss in appropriately selected patients [37].

For those who do not respond to first-line therapies, gonadotropins and assisted reproductive technologies (ART) represent effective alternatives, provided that therapeutic protocols are carefully optimized to balance efficacy with the minimization of iatrogenic risks [6]. In this context, GnRH antagonist protocols combined with agonist triggers and embryo cryopreservation have improved both the safety and success rates of in vitro fertilization (IVF) in women with high ovarian response [39].

Meanwhile, interest is growing in novel therapeutic strategies, including inositols and GLP-1 receptor agonists, as well as in advances in pharmacogenomics and personalized ovarian stimulation protocols that aim to refine fertility care in PCOS [38].

Equally important, lifestyle modification should be emphasized as a cornerstone of management, as even modest weight loss has been shown to restore ovulation and improve reproductive outcomes [4]. Lifestyle interventions additionally reduce metabolic and psychological burden, highlighting the need for integrating dietary, exercise, and behavioral strategies into routine fertility care [31].

At the same time, the psychological burden of PCOS remains underrecognized in fertility settings [7,12]. High rates of anxiety, depression, and body image dissatisfaction can undermine adherence and diminish clinical outcomes [7]. Thus, integrating psychological support within fertility care plans is essential for improving both reproductive success and overall well-being [36].

Given the multifactorial nature of PCOS, optimal care requires interdisciplinary coordination among reproductive endocrinologists, gynecologists, dietitians, and mental health professionals [36]. Ultimately, success in managing PCOS should be measured not only by conception, but also by achieving sustained hormonal balance, metabolic health, and emotional resilience [1]. A comprehensive, patient-centered model remains central to improving fertility outcomes and promoting long-term health in affected women [40].

Further randomized controlled trials are warranted to validate emerging treatments and refine predictive tools for treatment selection in PCOS-related infertility [41].

Author contributions
A G V conceptualized the topic, performed the literature review, and drafted and finalized the manuscript.

Conflicts of Interest
None to declare.

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