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# Evaluating the Role of Assisted Reproductive Technologies in Managing Infertility Associated with Polycystic Ovary Syndrome

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**Abstract**: **Background:** Polycystic ovary syndrome (PCOS) is the leading cause of anovulatory infertility, accounting for 70–80% of anovulatory cases worldwide. Reproductive failure reflects convergent dysregulation of hypothalamic-pituitary-ovarian signaling, AMH-mediated follicular arrest, insulin resistance-driven hyperandrogenism, impaired oocyte competence, and endometrial receptivity failure. When ovulation induction fails, assisted reproductive technology (ART) becomes the definitive intervention, though PCOS-specific biology necessitates individualized protocol modification. **Objective:** To critically evaluate the efficacy, safety, and emerging adjunctive strategies of ART in PCOS-associated infertility, emphasizing cumulative live birth rate (CLBR) and ovarian hyperstimulation syndrome (OHSS) as primary efficacy and safety endpoints. **Methods:** A structured narrative review was conducted per PRISMA 2020 guidelines, searching PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, and Web of Science (January 2000–March 2025) using MeSH/Emtree terms and free-text keywords across condition, intervention, and outcome domains. Eligible studies enrolled adult women (≥18 years) with confirmed PCOS (Rotterdam, AE-PCOS, or NIH criteria) undergoing ART, using RCT, cohort, case-control, systematic review, or meta-analytic designs. Following Zotero-based deduplication and dual-reviewer screening (Cohen's $\kappa = 0.84$), data were extracted using a standardized form. Methodological quality was appraised via RoB 2.0, Newcastle-Ottawa Scale, and AMSTAR-2, with GRADE-rated evidence certainty. Narrative synthesis was primary; random-effects (DerSimonian–Laird) pooling in RevMan 5.4 supplemented outcomes reported by ≥3 comparable studies. **Results:** Antagonist protocols with agonist triggering and freeze-all strategies eliminated late-onset OHSS while achieving CLBR comparable to normo-ovulatory populations. Frozen embryo transfer conferred superior CLBR and reduced OHSS versus fresh transfer; elective single embryo transfer reduced multiple pregnancy to 1–2% without compromising CLBR. **Conclusion:** Risk-stratified, phenotype-adapted ART achieves reproductive outcomes equivalent to normo-ovulatory populations when individualized protocols are systematically applied. Phenotype-stratified RCTs powered on CLBR remain a priority.

**Keywords:** Polycystic Ovary Syndrome; Assisted Reproductive Technology; IVF; ICSI; Frozen Embryo Transfer; Cumulative Live Birth Rate; Ovarian Hyperstimulation Syndrome.

## INTRODUCTION

Infertility is a significant global health challenge affecting millions of individuals and couples of reproductive age. According to the World Health Organization (WHO), approximately 17.5% of adults worldwide experience infertility at some point during their reproductive years, underscoring its substantial public health burden and the urgent need for effective fertility care strategies (World Health Organization [WHO], 2023). Beyond its medical implications, infertility is associated with profound psychological, social, and economic consequences, including anxiety, depression, marital stress, social stigma, and reduced quality of life. Consequently, infertility management remains a major priority within reproductive medicine and public health systems worldwide.

Among female infertility disorders, polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disorder affecting women of reproductive age and represents the leading cause of anovulatory infertility. The global prevalence of PCOS is estimated to range from 6% to 15%, depending on the diagnostic criteria employed and the characteristics of the studied population (Teede *et al*., 2023; Escobar-Morreale, 2018). The syndrome is characterized by a heterogeneous combination of reproductive, endocrine, metabolic, and psychological manifestations, including chronic oligo-anovulation, hyperandrogenism, polycystic ovarian morphology, insulin resistance, obesity, and metabolic dysfunction. This phenotypic heterogeneity contributes to substantial variation in reproductive outcomes and responses to fertility treatments among affected women.

Historically, infertility in PCOS was attributed primarily to chronic anovulation; however, contemporary evidence indicates that reproductive failure in PCOS reflects the convergence of several interacting biological layers, each of which is examined in depth in Section 3 of this review. At the genetic level, genome-wide association studies have identified more than a dozen susceptibility loci — including *DENND1A*, *LHCGR*, *FSHR*, *THADA*, and *YAP1* — with heritability estimates approaching 70%, supporting a polygenic model of

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disease susceptibility (Day *et al*., 2018). Superimposed on this genetic background, epigenetic mechanisms — altered DNA methylation patterns and dysregulated microRNAs (e.g., miR-21, miR-93, miR-320, let-7) and long non-coding RNAs such as *H19* and *MALAT1* — modulate granulosa and theca cell function, insulin signaling, and oocyte competence (Nasser *et al*., 2024). At the endocrine level, dysregulated AMH/AMHR2 signaling suppresses follicular FSH sensitivity, while LH hyperstimulation and insulin-resistance-driven hyperinsulinemia synergistically amplify ovarian androgen production, together producing follicular arrest and impaired oocyte maturation (Rosenfield & Ehrmann, 2016). These upstream abnormalities translate into oocyte-level consequences — mitochondrial dysfunction, oxidative stress, and altered cumulus-oocyte gene expression (Azziz *et al*., 2016) — and into impaired endometrial receptivity, marked by reduced *HOXA10/HOXA11*, integrin αvβ3, and LIF expression and by uterine microbiome alterations (Palomba *et al*., 2021; Nasser *et al*., 2024). Chronic low-grade inflammation and insulin resistance, present in 50–80% of affected women, further amplify this network and link reproductive and metabolic dysfunction (Teede *et al*., 2023).

Lifestyle modification and ovulation induction — using letrozole, clomiphene citrate, or gonadotropins — remain first-line treatments and successfully restore ovulation and achieve pregnancy in many women with PCOS. However, a substantial proportion of patients fail to conceive because of persistent anovulation, poor oocyte quality, advanced maternal age, male-factor infertility, tubal disease, or recurrent implantation failure, making assisted reproductive technologies (ART) — including intrauterine insemination (IUI), in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and frozen embryo transfer (FET) — indispensable to achieving pregnancy in this population. Over the past two decades, the introduction of GnRH antagonist protocols, GnRH agonist triggers, individualized ovarian stimulation regimens, vitrification, and freeze-all strategies has substantially reduced the incidence of ovarian hyperstimulation syndrome (OHSS), historically the most serious ART-related complication in PCOS, while advances in embryo culture, time-lapse imaging, and preimplantation genetic testing have improved embryo selection and cumulative live birth rates.

More recently, the emergence of precision reproductive medicine has expanded opportunities to individualize ART in PCOS. Artificial intelligence-based embryo selection platforms, machine learning models for OHSS risk prediction, metabolomic and proteomic biomarkers, endometrial receptivity testing, single-cell transcriptomics, and multi-omics integration are increasingly entering clinical and research use, offering tools to address the considerable biological heterogeneity that characterizes PCOS and to move toward genotype- and phenotype-informed treatment selection (Hanassab *et al*., 2024).

Despite this progress, important clinical challenges persist. Women with PCOS continue to face elevated risks of OHSS, miscarriage, gestational diabetes, hypertensive disorders of pregnancy, and adverse neonatal outcomes, and uncertainty remains regarding the optimal ART modality, stimulation strategy, embryo transfer approach, and adjunctive therapy for different PCOS phenotypes. The growing and increasingly molecular evidence base therefore requires a comprehensive, critical synthesis to guide evidence-based decision-making and to identify priorities for future research. Accordingly, the present review aims to critically evaluate the role of ART in managing PCOS-associated infertility: examining the molecular and pathophysiological mechanisms underlying this infertility, appraising the efficacy and safety of contemporary ART approaches, addressing major treatment-related challenges and complications, and exploring emerging therapeutic, technological, and precision-medicine strategies that may improve reproductive outcomes.

To ensure methodological transparency and reproducibility, a structured literature search was conducted using major biomedical databases, including PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library. Priority was given to randomized controlled trials, cohort studies, systematic reviews, meta-analyses, and international clinical practice guidelines published between 2000 and 2025. The review focuses on evidence related to PCOS pathophysiology, infertility mechanisms, assisted reproductive technologies, clinical outcomes, and emerging interventions relevant to reproductive medicine and molecular reproductive biology.

Figure 1 provides an overview of the search strategy for this synthesis, Figure 2 combines the

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molecular failure network, and Figure 3 transforms the molecular failure network into a clinical pathway.

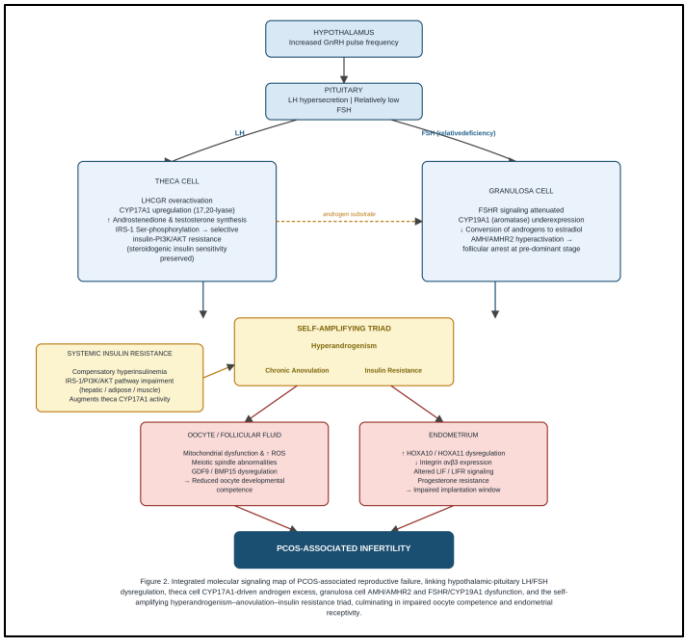



**Figure 1**: Integrated molecular signaling map of PCOS-associated reproductive failure, linking hypothalamic-pituitary LH/FSH dysregulation, theca-cell CYP17A1-driven androgen excess, granulosa-cell AMH/FSHR imbalance, insulin resistance, oocyte competence, and endometrial receptivity failure.

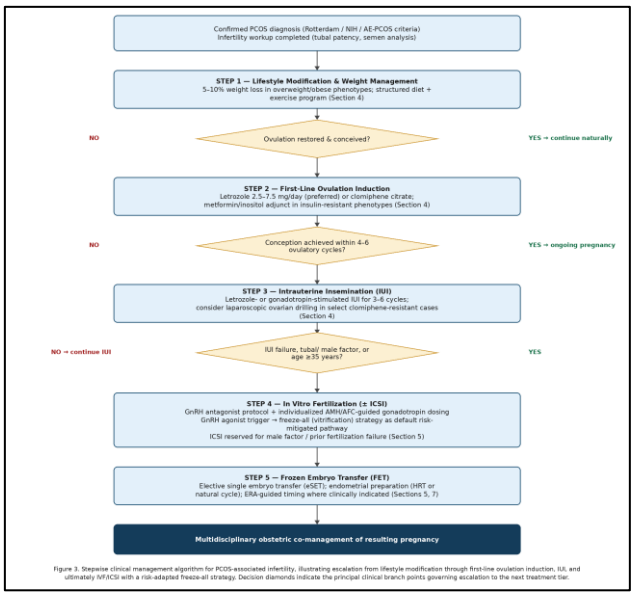



**Figure 2:** Stepwise clinical management algorithm for PCOS-associated infertility, illustrating escalation from lifestyle and ovulation induction to IUI, IVF, antagonist protocols, trigger selection, freeze-all, FET, and adjunctive therapies.

## METHODS

This manuscript reports a structured narrative review employing a pre-defined systematic search strategy, designed to critically synthesize the published evidence on ART in PCOS-associated infertility. Reporting conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines as a transparency and reproducibility framework (Page *et al.*, 2021). Consistent with the narrative synthesis design, formal meta-analytic pooling was not the primary analytical strategy, given anticipated heterogeneity in PCOS diagnostic criteria, phenotype distribution, stimulation protocols, trigger strategies, embryo transfer approaches, and outcome definitions across the eligible literature. When available, RCTs and

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meta-analyses of RCTs were afforded greater evidentiary weight than observational studies in the evidence hierarchy. The review was structured to address four a priori research questions: (a) What is the molecular, genetic, and epigenetic basis of reproductive failure in women with PCOS? (b) What are the comparative efficacies of ART modalities in this population? (c) What evidence-based, PCOS-specific risk mitigation strategies exist during ART? (d) What emerging pharmacological, AI-assisted, and omics-based adjuncts are available for ART optimization?

Data were collected exclusively from published peer-reviewed literature through systematic electronic database searching, supplemented by manual reference list checking and forward citation tracking. No unpublished data, grey literature, conference proceedings, or personal communications were included in the evidence base. A systematic literature search was independently conducted across five major electronic databases: PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science Core Collection, covering publications indexed between January 2000 and March 2025. The lower date boundary was selected to align with the introduction of the Rotterdam diagnostic consensus, which established a uniform international PCOS definition (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). No language restriction was applied, provided that full-text translations were obtainable.

Search strategies were constructed separately for each database, combining controlled vocabulary (MeSH terms in PubMed/MEDLINE; Emtree terms in Embase) with free-text keywords across three conceptual domains — condition (PCOS and related terminology), intervention (ART modalities), and outcome (reproductive outcomes) — linked using Boolean operators AND and OR, with truncation (*) and wildcard (?) characters to capture spelling variants. The core search string integrated terms for PCOS, ART modalities (IVF, ICSI, IUI, frozen embryo transfer, ovulation induction, controlled ovarian hyperstimulation), and reproductive outcomes; database-adapted strings were applied consistently across all five platforms. To supplement electronic searching, reference lists of all included studies and high-impact prior reviews were hand-searched, and forward citation tracking was performed in Scopus to capture studies citing key landmark RCTs and international guidelines.

All search results were exported from each database in RIS format and imported into Zotero reference management software (v6.0) for centralized record management and algorithmic deduplication prior to screening. Both searches and deduplication were independently verified by a second reviewer to ensure completeness and reproducibility.

The unit of analysis in this review was the individual study participant as defined within each included primary or secondary study. Eligible respondents were adult women aged ≥18 years with a confirmed diagnosis of PCOS according to at least one of three internationally recognized diagnostic frameworks: the Rotterdam (2003) consensus criteria (requiring two of three features: oligo-anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound), the Androgen Excess and PCOS Society (AE-PCOS) criteria, or the NIH 1990 criteria.

No restriction was applied to PCOS phenotypic sub-classification (phenotypes A–D under Rotterdam criteria), age within the adult range, body mass index, ethnicity, or country of origin, in order to preserve representativeness across the full phenotypic spectrum of PCOS. Studies enrolling mixed populations (PCOS and non-PCOS participants) were eligible provided that PCOS-specific subgroup data were reported separately and extractable without imputation or assumption.

The aggregate respondent pool across all included studies comprised women undergoing at least one ART modality, spanning diverse clinical settings, geographic regions, healthcare systems, and PCOS phenotypic presentations. Across the included evidence base, enrolled respondents ranged from young adults with classic hyperandrogenic-anovulatory PCOS to older women with milder phenotypes, including those with insulin resistance, obesity, and metabolic comorbidities, reflecting the real-world heterogeneity of the PCOS population presenting for fertility treatment.

Studies were eligible for inclusion if all five of the following criteria were satisfied:
(a) The study design was an RCT, quasi-RCT, prospective or retrospective cohort study, case-control study, systematic review, or meta-analysis;
(b) Enrolled participants met at least one of the three recognized PCOS diagnostic criteria

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(Rotterdam 2003, AE-PCOS Society, or NIH 1990);
(c) The intervention involved at least one ART modality — intrauterine insemination (IUI), conventional IVF, intracytoplasmic sperm injection (ICSI), fresh or frozen-thawed embryo transfer (FET), vitrification-based freeze-all strategy, or oocyte cryopreservation;
(d) At least one quantitative reproductive, obstetric, or safety outcome was reported with calculable event rates or effect estimates with associated measures of precision (standard deviations, confidence intervals, or p-values); and
(e) The article was published as a full-text, peer-reviewed paper within the specified date range (January 2000 – March 2025).

Studies were excluded if they met any of the following criteria:
(a) Enrolled exclusively non-PCOS populations without extractable PCOS-specific subgroup data;
(b) Were limited to case reports, conference abstracts, letters, editorials, or expert commentaries without primary outcome data;
(c) Reported exclusively in vitro or animal-model data without human clinical outcomes;
(d) Employed non-standardized, self-defined, or unspecified PCOS diagnostic criteria that could not be mapped to any of the three recognized frameworks; or
(e) Reported only raw outcome counts without calculable event rates, effect estimates, or measures of precision.
Retrieved records were imported into Zotero reference management software (v6.0) and subjected to algorithmic deduplication prior to screening. Study selection proceeded in two sequential phases: (i) title and abstract screening against the pre-specified eligibility criteria, followed by (ii) full-text eligibility assessment using a pre-piloted, standardized eligibility checklist. Both phases were conducted independently by two reviewers; disagreements were resolved by consensus discussion, with recourse to adjudication by a third reviewer where consensus was not achievable. Interrater agreement across both phases was quantified using Cohen's kappa coefficient ($\kappa = 0.84$), indicating near-perfect agreement (Landis & Koch, 1977). The complete study selection process, including records identified per database, duplicates removed, records excluded at title and abstract stage, and full-text exclusions with reasons, is documented in the PRISMA 2020 flow diagram (Figure 1).

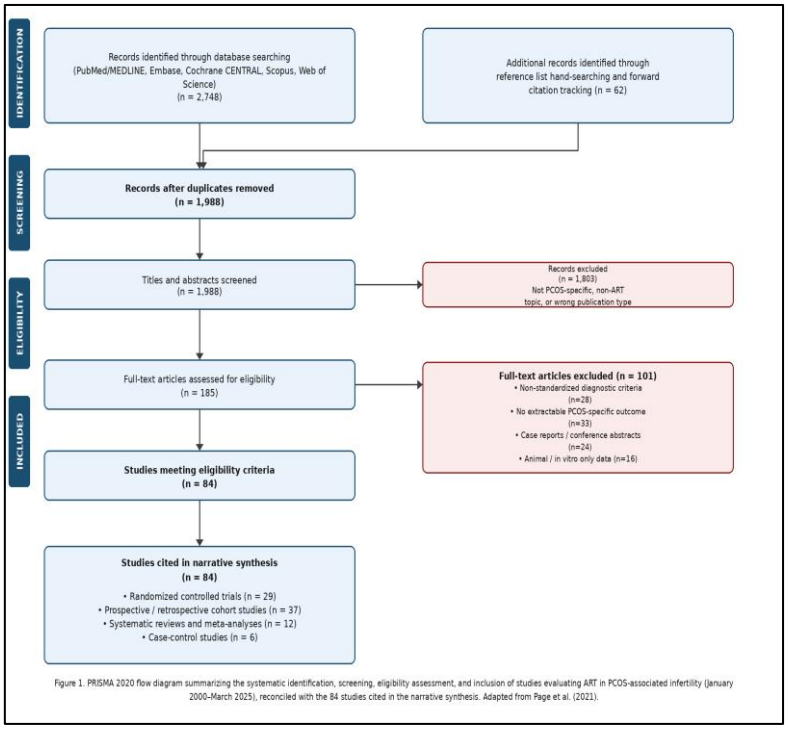



**Figure 3**: PRISMA 2020 flow diagram summarizing the systematic identification, screening, eligibility assessment, and inclusion of studies evaluating ART in PCOS-associated infertility.

Data extraction was performed in duplicate by two independent reviewers using a standardized extraction form developed a priori and pilot-tested on five randomly selected eligible studies prior to full-scale application. The form was revised for

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clarity and completeness based on pilot findings before extraction commenced. Discrepancies between extractors were identified through systematic comparison and resolved by consensus discussion; where consensus was not achievable, a third reviewer adjudicated.

The extraction form captured the following pre-specified domains:
*Study-level characteristics:* first author, year of publication, country of origin, journal, study design, total sample size, follow-up duration, and funding source.

*Population characteristics:* participant age (mean ± SD or range), body mass index, PCOS diagnostic criteria applied, phenotype distribution where reported, duration of infertility, and baseline endocrine parameters including serum anti-Müllerian hormone (AMH), antral follicle count (AFC), LH/FSH ratio, total testosterone, and homeostatic model assessment of insulin resistance (HOMA-IR).

*Intervention parameters:* ART modality, gonadotropin type and starting dose, stimulation protocol (GnRH agonist long or short protocol, GnRH antagonist protocol), antagonist initiation strategy (fixed vs. flexible), trigger agent type (HCG, GnRH agonist, dual trigger, kisspeptin), insemination method (conventional IVF vs. ICSI), embryo culture duration (Day 3 cleavage vs. Day 5/6 blastocyst), cryopreservation method (slow-freeze vs. vitrification), FET protocol and endometrial preparation strategy, and adjunctive therapies (metformin, inositol, GLP-1 receptor agonists, cabergoline, dopamine agonists).

*Outcome data:* all primary and secondary outcomes with their operational definitions, measurement timepoints, denominators, and effect estimates with 95% confidence intervals where reported.

*Potential confounders and effect modifiers:* co-interventions, male-factor exclusion or inclusion criteria, PCOS phenotype distribution, laboratory quality indicators, and cycle cancellation rates.

Following extraction, all data were organized into structured evidence tables stratified by the four a priori research questions, providing a systematic overview of the available evidence base prior to synthesis.

The following validated instruments and software platforms were employed in the data analysis process:

*Narrative synthesis framework:* Structured narrative synthesis was operationalized following the EPPI-Centre guidance on narrative synthesis in systematic reviews and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins *et al*., 2024).

*Risk of bias appraisal:* Three design-matched instruments were applied: the Cochrane Risk of Bias 2.0 (RoB 2) tool for RCTs (Sterne *et al*., 2019); the Newcastle-Ottawa Scale (NOS) for observational cohort and case-control studies (Wells *et al*., 2011); and AMSTAR-2 for included systematic reviews and meta-analyses (Shea *et al*., 2017). Risk-of-bias assessments were performed independently by two reviewers and discrepancies resolved by consensus.

*Evidence certainty rating:* The GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework (Guyatt *et al*., 2011) was applied to rate the overall certainty of evidence for each primary outcome domain.

*Statistical software for quantitative pooling:* Where quantitative pooling was performed, analyses were conducted using RevMan 5.4 (Review Manager, Cochrane Collaboration, Copenhagen).

*Reference management and deduplication:* Zotero reference management software (v6.0) was used for record management, deduplication, and citation tracking.

*Interrater agreement:* Cohen's kappa coefficient ($\kappa$) was calculated to quantify the level of agreement between reviewers at both title/abstract and full-text screening stages.

The primary analytical technique was structured narrative synthesis, selected a priori given the anticipated heterogeneity across diagnostic criteria, phenotypes, stimulation protocols, trigger strategies, and outcome definitions in the eligible literature. Narrative synthesis was conducted in four sequential analytical steps following the EPPI-Centre framework (Higgins *et al*., 2024):
(i) *Preliminary synthesis* — tabular and descriptive summary of study characteristics, populations, interventions, and outcomes for each of the four a priori research questions;
(ii) *Exploration of relationships* — direct comparison and juxtaposition of outcome data across ART modality, PCOS phenotype subgroup, stimulation protocol, and trigger type to identify

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patterns, consistencies, and sources of heterogeneity;
(iii) *Robustness assessment* — evaluation of the influence of study quality, risk of bias, and methodological variation on the consistency and direction of synthesized findings, with explicit flagging of studies at high risk of bias; and
(iv) *Evidence synthesis* — integration of findings across subgroups into coherent, GRADE-rated evidence statements for each primary and secondary outcome domain.

Where three or more studies reported a common outcome using comparable definitions and comparator groups, quantitative pooling was applied as a supplementary analytical technique. For pooled analyses, binary outcomes were expressed as odds ratios (OR) or risk ratios (RR) with 95% confidence intervals (CIs); continuous outcomes were expressed as mean differences (MD) or standardized mean differences (SMD) with 95% CIs. Statistical heterogeneity was quantified using the $I^2$ statistic and Cochran's Q test; $I^2$ values of 25%, 50%, and 75% were interpreted as low, moderate, and substantial heterogeneity, respectively. A random-effects model using the DerSimonian–Laird method was applied for all pooled analyses to account for anticipated between-study clinical and statistical variance. All pooled effect estimates are reported with 95% confidence intervals.

The data analysis process proceeded through the following six sequential steps:
**Step 1 — Data organization and tabulation:** Following completion of data extraction, all extracted data were transferred into structured evidence tables organized by the four a priori research questions. Each evidence table captured study identity, design, population characteristics, intervention parameters, comparator, and all reported primary and secondary outcomes, providing a comprehensive and systematic overview of the available evidence base prior to any analytical synthesis.

**Step 2 — Quality weighting and risk-of-bias integration:** Risk-of-bias assessments were completed independently by two reviewers for all included studies using the appropriate design-matched appraisal tool (RoB 2 for RCTs, NOS for observational studies, AMSTAR-2 for systematic reviews). Assessment results were tabulated alongside extracted outcome data. Studies rated as having high or unclear risk of bias were assigned lower evidentiary weight within the narrative synthesis and are explicitly identified wherever their findings are incorporated into evidence statements throughout the results sections.

**Step 3 — Narrative synthesis and evidence statement drafting:** Synthesized findings were organized thematically across the four research domains. For each domain, evidence statements were drafted summarizing the direction, consistency, magnitude, and clinical relevance of findings across included studies. Where studies reported discordant findings, these were noted explicitly and explored in relation to methodological differences, population heterogeneity, protocol variation, and risk-of-bias profiles.

**Step 4 — Subgroup analyses:** Pre-specified subgroup analyses were conducted where sufficient data permitted, stratified by: PCOS diagnostic criterion applied (Rotterdam 2003 vs. NIH 1990 vs. AE-PCOS Society); PCOS phenotypic sub-classification (phenotypes A–D under Rotterdam criteria); body mass index category (normal weight, overweight, obese); stimulation protocol type (GnRH agonist long protocol vs. GnRH antagonist protocol); trigger agent type (HCG vs. GnRH agonist vs. dual trigger); and embryo transfer strategy (fresh transfer vs. freeze-all with deferred FET). Subgroup findings were integrated into the narrative synthesis to contextualize between-study heterogeneity and identify phenotype-specific treatment effects.

**Step 5 — Sensitivity analyses:** Sensitivity analyses were performed by sequentially excluding studies at high risk of bias and re-evaluating the direction, magnitude, and consistency of synthesized findings. This step was designed to assess the robustness of primary evidence statements and to determine whether conclusions were disproportionately influenced by methodologically weaker studies. Where sensitivity analyses materially altered the interpretation of findings, this is explicitly noted in the results sections.

**Step 6 — GRADE evidence rating:** For each primary and secondary outcome domain, overall evidence certainty was rated using the GRADE framework by two independent reviewers across five pre-specified domain-level assessments: (i) risk of bias across included studies; (ii) inconsistency in direction or magnitude of effects; (iii) indirectness of the available evidence relative

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to the review population and outcomes; (iv) imprecision of effect estimates; and (v) likelihood of publication bias. Evidence certainty was classified as high, moderate, low, or very low. Final GRADE ratings were agreed by consensus and are integrated into the narrative synthesis throughout the results sections to contextualize the strength of each evidence statement and guide clinical interpretation.

Consistent with the 2020 ESHRE IVF/ICSI stimulation guideline and the 2023 International Evidence-Based PCOS Guidelines (Bosch *et al*., 2020; Teede *et al*., 2023), cumulative live birth rate (CLBR) per initiated ovarian stimulation cycle was designated the primary efficacy outcome. CLBR was defined as the proportion of initiated stimulation cycles resulting in at least one live birth following all fresh and frozen embryo transfers derived from that cycle. Where CLBR was not reported, live birth rate per transfer or clinical pregnancy rate was used as a prespecified surrogate outcome and is explicitly identified as such throughout the narrative synthesis.

The primary safety outcome was OHSS incidence and severity, classified according to the 2016 ASRM classification system (Practice Committee of the American Society for Reproductive Medicine, 2016), which distinguishes early from late OHSS and grades severity as mild, moderate, or severe.

Secondary outcomes included: miscarriage rate (defined as pregnancy loss before 20 completed weeks of gestation), ectopic pregnancy rate, multiple pregnancy rate, total gonadotropin consumption (IU), total oocyte yield, mature (MII) oocyte count, fertilization rate, blastulation rate, embryo utilization rate, and neonatal outcomes (birth weight, gestational age at delivery, preterm delivery rate defined as delivery before 37 completed weeks, and neonatal intensive care unit admission rate) where reported by included studies.

## MOLECULAR PATHOPHYSIOLOGY RELEVANT TO ART

Although often referred to as anovulation, a more comprehensive molecular phenotype involving the hypothalamic-pituitary-ovarian axis, the follicular microenvironment, the oocyte and the endometrium influences ART outcome. Genome-wide association studies have identified genes that directly influence reproduction (such as LHCGR/FSHR, THADA, DENND1A, YAP1, INSR, and FTO) that are associated with susceptibility to PCOS (Chen *et al*., 2011; Day *et al*., 2018; Shi *et al*., 2012). The DENND1A.V2 isoform, when overexpressed in theca cells, induces a steroidogenic program similar to that observed in PCOS, characterized by increased expression of both CYP17A1 and CYP11A1 and STAR (McAllister *et al*., 2015), making it a functional driver of autonomous androgen production. Recent clustering also indicates two distinct biological subtypes of PCOS: hyperandrogenic (lean) and insulin-resistant (obese), which could explain why some lean and obese patients with PCOS may not respond to treatment in the same way (Dapas *et al*., 2020).

Genetic architecture also helps to understand why PCOS cannot be simply summarized as obesity or insulin resistance. Variants in LHCGR and FSHR are associated with gonadotropin sensitivity, DENND1A is associated with vesicular trafficking and steroidogenic identity in theca cells, INSR is associated with insulin signaling, and FTO is associated with adiposity and metabolic severity. These pathways come together at the ovary, but are from different biological levels. In ART, this translates to two patients with the same AFC having different androgen excess, insulin exposure, endometrial phenotype and stimulation risk. Endocrine phenotype should therefore be considered as well as ovarian reserve in future protocols.

The four practical axes for phenotype stratification are: reproductive severity, metabolic severity, ovarian response potential, and uterine risk. Reproductive severity is a measure of anovulation, androgen excess, LH/FSH imbalance and the duration of infertility. The metabolic severity corresponds to BMI, insulin resistance, dyslipidaemia, blood pressure and glucose tolerance. Ovarian response potential is related to AMH, AFC, age and prior stimulation. Uterine risk is related to chronic anovulation, endometrial thickness, progesterone exposure, uterine pathology, miscarriage history and FET preparation. The axes are more useful for ART planning than just phenotype letters.

The second layer of heterogeneity is provided by epigenetic programming. In animal models, prenatal exposure to androgens causes hyperpulsatility of LH in adults, ovarian follicular arrest, insulin resistance and changes in reproductive behavior (Risal *et al*., 2019). The models proposed here indicate that the features of

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PCOS may be fixed prior to the onset of adult lifestyle-related factors. Developmental continuity is also suggested by elevated AMH and androgen exposure of daughters of affected mothers, although this evidence is less direct. While ART cannot prevent this origin, the awareness of epigenetic susceptibility highlights the need for avoiding unnecessary supraphysiologic exposures during stimulation, transfer and early pregnancy.

The neuroendocrine level, increased GnRH pulsatility, is a factor that promotes LH over FSH production. LH stimulates LHCGR on theca cells, leading to an increase in the activity of cAMP/PKA/CREB, which in turn increases StAR, CYP11A1, HSD3B2 and particularly CYP17A1 activity. CYP17A1 has 17-alpha-hydroxylase and 17,20-lyase activity, and cytochrome b5 specifically increases androgenic flux towards androstenedione. With androgen excess, there is a decrease in normal progestin negative feedback to GnRH pulsatility, which maintains the LH-dominant state. This cycle helps to explain why some women have chronic anovulation and why there is a tendency to high follicular recruitment during stimulation (Rosenfield & Ehrmann, 2016).

The follicular effect of excess LH is not just excess androgen, it is a disruption of paracrine communication. Androgens from theca cells first promote granulosa-cell responsiveness to FSH, but chronic excess causes the follicle to become arrested, the overproduction of AMH, and reduced aromatase activity. Granulosa cells cultured in the presence of chronic androgen and insulin exposure exhibit abnormal expression of steroidogenic enzymes, impaired apoptosis, and impaired granulosa cell differentiation. This results in a large number of follicles that are recruited but in varying competence. Exogenous FSH can be used to restore growth during IVF, but may not restore the cytoplasmic maturation program that was disrupted prior to the onset of stimulation.

This is amplified by a selective signaling defect, insulin resistance. Serine phosphorylation of IRS-1 by kinases like JNK, IKK beta, mTOR and p70S6K disrupts the PI3K/AKT metabolic branch of insulin signaling, thereby decreasing GLUT4 translocation and increasing systemic hyperinsulinemia in PCOS. However, mitogenic MAPK/ERK signaling is still sufficient to allow insulin to enhance theca-cell steroidogenesis, LHCGR expression, and CYP17A1 transcription. This leads to a paradoxical situation: the ovary is insulin-sensitive while the organism is insulin-resistant (McAllister *et al*., 2015; Rosenfield & Ehrmann, 2016). This is why metformin and weightloss can increase stimulation safety and function of ovulation, but cannot completely normalize ART risk in all phenotypes.

The metabolic part is also in the endometrial tissue. Hyperinsulinemia may stimulate endometrial AKT, change the localization of FOXO1 and limit decidualization despite normal serum progesterone levels. Adipose inflammation leads to elevated levels of TNF-alpha, IL-6 and CRP, which can affect receptivity, vascular function and trophoblast invasion. These mechanisms account for the fact that BMI adjustment reduces, but does not remove, excess miscarriage and obstetric risk in PCOS cohorts. The clinical implication is that metabolic optimization should be based on insulin resistance, glycemic status, blood pressure, and inflammatory risk factors, not just weight.

AMH is a marker and mediator of the follicular state of PCOS. The number of small antral follicles is larger and they produce AMH at 2-5 times the concentration of normo-ovulatory controls, and androgen signaling can upregulate AMH production per follicle. The activation of AMH/AMHR2 signaling pathway inhibits the expression of CYP19A1 aromatase and FSHR in granulosa cells and decreases the production of estradiol and the sensitivity of granulosa cells to FSH. The clinical correlate is follicular arrest - many follicles are seen and few are selected for dominance without pharmacologic intervention (Dewailly *et al*., 2016). Thus, in ART, AMH and AFC double up as a predictor of ovarian reserve and a marker of risk of excessive response and OHSS.

The yield-competence paradox is the phenotype of the oocyte in PCOS. IVF is known to collect a higher number of oocytes from PCOS ovaries, however, the oocytes may be less competent due to oxidative stress in follicles, mitochondrial dysfunction, impaired cumulus-oocyte signaling, and meiotic fragility. In PCOS, there is an increase in ROS and decrease in antioxidant activity in the follicular fluid, and the oocytes may have impaired mitochondrial membrane potential, abnormal cristae, decreased ATP production, and spindle stress. Altered expression of PTGS2, HAS2, TNFAIP6, GDF9 and BMP15 signaling nodes, which are involved in the regulation of cytoplasmic maturation and formation of cumulus matrix, may also impair cumulus expansion

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(Dumesic *et al*., 2015; Hernandez-Gonzalez *et al*., 2006). These mechanisms are not an obstacle to good embryo cohorts, but rather account for why the number of oocytes is not a good endpoint.

This is particularly important as mitochondrial function is crucial in meiosis, fertilization, pronuclear formation and early cleavage all rely on maternal ATP stores prior to activation of the embryonic genome. A decrease in mitochondrial membrane potential may lead to defects in spindle assembly and to defects in chromosome segregation; damage of mitochondrial DNA by oxidative stress may aggravate electron-transport deficiencies. The pathways linking metabolic stress to aneuploidy of the embryo are likely to be through cohesin and spindle-checkpoint vulnerability, but age is the primary factor. This makes biological appeal of protocol strategies that lower excessive stimulation, oxidative burden, and extended culture stress, even in the absence of definitive proof of live-birth, attractive.

Cumulus cells are useful translational reporters as they can be removed during ICSI or denudation and profiled without any damage to the embryo. The expression of genes that alter cumulus hyaluronan matrix formation, prostaglandin signaling, EGFR response, glucose metabolism, and apoptosis may help to identify oocytes with decreased competence in PCOS. The second major molecular bottleneck is endometrial receptivity. The endometrium of women with PCOS can exhibit androgen-mediated suppression of HOXA10 and HOXA11, decreased expression of integrin alpha-v-beta-3, impaired pinopode formation, reduced LIF/LIFR/gp130-JAK/STAT3 signaling, progesterone receptor isoform imbalance, altered FOXO1-mediated decidualization, and low-grade inflammatory changes associated with uterine natural killer cells and cytokine polarization (Cermik *et al*., 2003; Lessey & Young, 2019; Palomba *et al*., 2021; Savaris *et al*., 2011). Controlled ovarian stimulation is a second insult because it causes an increase in the level of estrogen and an early exposure to progesterone, which may accelerate the maturation of the endometrium in relation to embryo development. This is the mechanism of freeze-all in high-risk cycles with PCOS.

This bottleneck is linked to resistance to progesterone. Estrogen priming of progesterone action, PR-B-induced decidual gene transcription, FOXO1 nuclear activity, IGFBP-1 and prolactin expression, immune tolerance, and epithelial adhesion molecule expression are all necessary for normal implantation. In PCOS, increased activity of the androgen receptor and insulin-AKT signaling may result in higher proportion of PR-A, reduced nuclear PR-B transcriptional activity and nuclear exclusion of FOXO1. The uterus can then appear to have a lack of progesterone signaling even though there is enough circulating progesterone. This concept is important for careful luteal support, avoiding advanced endometrium in fresh cycles and research into the duration of progesterone in PCOS cycles for FET.

The immune dimension is not a theory of implantation, but a part of decidual physiology. The invasion and remodeling of the spiral arteries are coordinated by uterine natural killer cells, macrophages, regulatory T cells and trophoblast HLA interactions. This balance can be altered in the direction of shallow invasion or abnormal vascular adaptation due to inflammation and hyperandrogenism associated with PCOS. This may be a link between early implantation failure and later hypertensive disease. Hence, the pregnancy outcomes following ART in PCOS should be monitored beyond the live birth to include preeclampsia, fetal growth, placentation markers, and neonatal morbidity.

New data also suggest that non-coding RNAs, epigenetic programming, and microbiome-immune interactions are all involved. Increased or decreased expression of miR-93, miR-21, miR-146a, MALAT1, and H19 has been found in granulosa cells, follicular fluid, or circulation, which suggests that these microRNAs are involved in post-transcriptional regulation of steroidogenesis, inflammation, and oocyte quality (Murri *et al*., 2013; Sang *et al*., 2013). Developmental programming of prenatal androgen exposure results in adult PCOS-like reproductive and metabolic traits, and daughters of PCOS-affected mothers may have altered AMH exposure and increased future risk. These observations are more relevant to future stratification than to current ART decisions, but support the use of phenotype-aware trial design.

## CONVENTIONAL TREATMENT BEFORE ART

Pre-ART management should not delay definitive ART when age and/or other factors affecting fertility make this a bad idea, but should correct modifiable metabolic and endocrine drivers. A 5-10% weight loss may restore ovulation in many overweight and obese PCOS patients and enhance

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insulin sensitivity, androgen levels and sensitivity to ovulation induction (Lim *et al*., 2019; Teede *et al*., 2023). At a molecular level, diminished visceral adiposity leads to enhanced adiponectin-AMPK signaling, suppression of inflammatory kinase activation, diminished serine phosphorylation of IRS-1, and diminished compensatory hyperinsulinemia. The benefits are greatest if lifestyle intervention is structured, time-limited, and coupled to reproductive planning, not as an indefinite prerequisite.

Timing is crucial. The need for extended weight loss prior to ART may diminish cumulative chance of live birth in older patients by "sacrificing" reproductive time. A rational approach is to establish a short window of metabolic optimization (typically three to six months, depending on age) with measurable outcomes: weight loss (if indicated), improvement in HbA1c and fasting insulin, blood pressure control, smoking cessation, folate supplementation, assessment of sleep apnea, and medication review. If the patient is obese or diabetic, more intensive preparation may be necessary, but the intervention should be reproductive-medicine specific and not a general lifestyle instruction.

Letrozole is the drug of choice for the initial use as an ovulation-inducing drug. It is a reversible inhibitor of the enzyme CYP19A1 (aromatase) that decreases the feedback of estradiol and elevates endogenous FSH sufficiently to recruit a dominant follicle. It also transiently increases intrafollicular androgen, which may increase granulosa-cell FSHR expression and help to make follicles responsive. Letrozole resulted in more live births than clomiphene citrate in the PPCOS II trial, but did not increase congenital anomalies (Legro *et al*., 2014). Clomiphene is still useful when letrozole is not available; its long-acting estrogen-receptor antagonism may be responsible for the difference in ovulation rates and live-birth rates, because it may inhibit endometrial proliferation and cervical mucus (Brown & Farquhar, 2016).

The clinical relevance of the superiority of letrozole to ART is that there is no need to escalate unnecessary care and treatment, while cycles that fail with letrozole indicate patients who need more intensive care. High BMI, high AMH, severe hyperandrogenism and insulin resistance are all the factors that predict complex IVF stimulation and increase the risk of letrozole resistance. Thus, response to oral ovulation induction should not be considered as a failed step, but rather as phenotypic information when considering ART planning.

Gonadotropin ovulation induction can be used after the failure of the oral agents, but because the gonadotropin dose-response curve for PCOS is narrow, low dose-step up protocols are necessary. After passing the threshold, several follicles can grow at the same time. Low starting doses (37.5-50 IU/day) with careful dose increases and strict cancellation guidelines minimize multiple pregnancy and OHSS risk. Laparoscopic ovarian drilling is a limited second-line treatment option that reduces androgen production and AMH levels and is a viable alternative to gonadotropins for restoring ovulation when intensive monitoring is challenging, and with a lower risk of multiple pregnancies (Amer *et al*., 2009). Metformin is not as effective as letrozole alone for fertility therapy, but may decrease insulin exposure, androgen excess, and risk of OHSS when used in conjunction with insulin-resistant or high-response phenotypes (Tang *et al*., 2012; Palomba *et al*., 2013). Combination of myo-inositol may enhance insulin second messenger signaling and follicular competence, but the quality of trials is variable (Unfer *et al*., 2012).

The choice to proceed from induction of ovulation to IVF should be clear. Multiple pregnancy and emotional burden, cost, and repeated low probability cycles may occur without any improvement in final outcome. IVF is more efficient in the following cases: when the duration of infertility is long, when the number of sperm after washing is low, when there is co-existence of endometriosis or tubal disease, when the age is more than 35 years, when multifollicular cancellation occurs after repeated stimulation. In this regard, IVF is not necessarily more aggressive; in high-risk PCOS, it can be safer than repeated gonadotropin-IUI as the number of embryos can be managed with eSET.

## ART MODALITIES AND PROTOCOL DESIGN

IUI is the least invasive ART and is reasonable for PCOS patients who have patent tubes, good post-wash TMC, and ovulation following letrozole or low dose gonadotropins. The plus side is the cost and ease of access, while the downside is a lesser efficacy per cycle and increased multiple-gestation risk with multifollicular stimulation. The success of IVF is reported as cumulative live birth after 3-6 cycles, typically between 15-25%, and with diminishing returns after about 4 well conducted

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cycles (Cohlen *et al*., 2018). IUI should be time-limited, especially in the case of women over 35 years of age or those who have been infertile for a long period.

IUI protocols should avoid using PCOS biology against the patient. The gonadotropin stimulated IUI can create two to four follicles, increasing the chances of pregnancy, but also the risk of twins and higher-order multiples. Due to the quick recruitment of patients with PCOS, the thresholds for ultrasound monitoring and cancellation should be set high. For many, Letrozole-IUI is preferred due to its higher chances of mono- or bifollicular development. Luteal support may be considered after triggered cycles, but cannot be used to make up for too many follicles.

IVF is the main ART technique used in the case of ovulation-induction failure, tubal factor infertility, moderate infertility duration, advanced maternal age, and multiple IUI failure. The choice of laboratory insemination method is not as significant as the design of the protocol in PCOS. The long GnRH-agonist downregulation protocol, which is traditionally used in IVF, results in a significant suppression of the pituitary gland and may necessitate increased gonadotropins, synchronous recruitment of follicles, elevated levels of estradiol, and increased mass of luteinized granulosa cells. This puts the patient at a higher risk for OHSS and is no longer the recommended default treatment for PCOS.

The first step of a practical PCOS IVF plan is before stimulation. Baseline AMH and AFC are used to define response risk, BMI, HbA1c, fasting glucose or insulin, blood pressure, and androgen indices are used to define metabolic and obstetric risk, semen analysis is used to decide IVF vs. ICSI, uterine imaging is used to identify polyps, fibroids, adhesions, or hydrosalpinx, and counseling is used to determine the likelihood of freeze-all. This is an important pre-cycle discussion because patients might feel they are being failed to transfer if they do not.

GnRH-antagonist protocols are preferred because the use of either cetrorelix or ganirelix causes a fast suppression of LH, via competitive receptor blockade rather than receptor internalization. The pituitary is still capable of reacting to a single bolus of GnRH, and an endogenous LH/FSH surge will occur resulting in the maturation of oocytes, but the luteotropic effect of this surge is less than that of HCG. The main pharmacologic difference is that HCG has a longer half-life and maintains higher levels of LHCGR activation, which leads to increased granulosa-lutein VEGF-A transcription, whereas agonist trigger significantly reduces the risk of late OHSS in antagonist cycles (Al-Inany *et al*., 2016; Bosch *et al*., 2020; Youssef *et al*., 2014). These protocol decisions are shown in the sequential ART workflow in Figure 4.

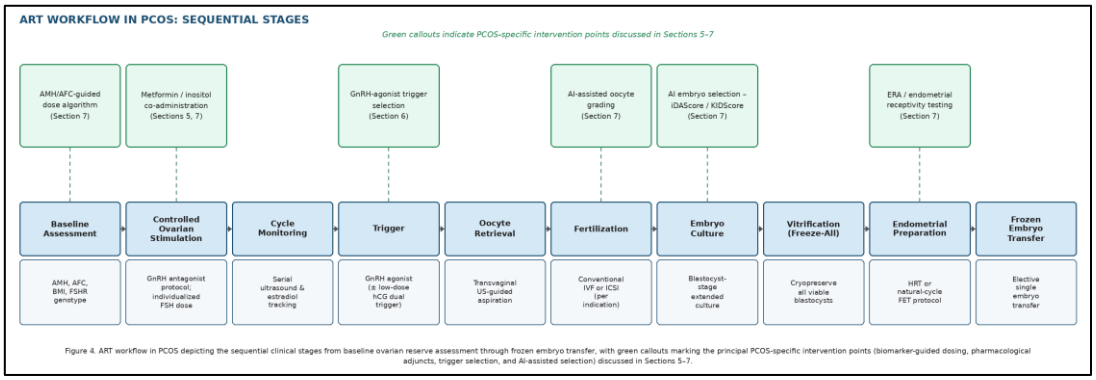



**Figure 4:** ART workflow in PCOS across sequential stages from baseline assessment through stimulation, trigger, retrieval, insemination, embryo culture, vitrification, transfer, and pregnancy follow-up.

The initial dose of gonadotropins should be tailored to age, BMI, AMH, AFC, previous response and phenotype. High AMH and AFC indicate predisposition to oocytes and OHSS and should result in low starting dose, early monitoring and low threshold for agonist trigger and freeze-all. In high response PCOS patients, mild stimulation may be indicated as the goal is not to retrieve as many oocytes as possible, but to obtain an appropriate number of mature and developmentally competent oocytes with safe endocrine exposure. If the response is poor or unexpectedly low, in poor or unexpectedly low responders with PCOS overcorrection should be

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avoided; the same syndrome may be associated with age-related reserve decline.

Rather than a single estradiol level, monitoring should be done by observing the trajectory. Rapid follicle recruitment, high number of intermediate follicles, steep rise in estradiol and symptoms are more informative than the lead follicle. Timing should be a compromise between the number of mature oocytes collected and the number of small follicles collected late. Coasting is not as popular as antagonist/agonist-trigger/freeze-all strategies as it can have a negative effect on oocyte competence and is not used to treat all OHSS pathways. The best current practice is prevention instead of rescue.

There are different methods of managing the luteal phase depending on the trigger and transfer plan. HCG trigger and fresh transfer will need conventional luteal support and will be at risk for OHSS. Intensive luteal rescue with progesterone, estradiol and sometimes low dose HCG is needed for fresh transfer, and may re-introduce the risk of OHSS. In high-risk PCOS, the best safety plan is to use agonist trigger followed by freeze-all, which eliminates this trade-off. Deferred FET is a change in luteal support from rescue of a sub-optimal luteal phase to optimization of a planned luteal phase.

ICSI should be used in male factor infertility, prior failure in fertilization, surgically retrieved sperm, severe teratozoospermia and preimplantation genetic testing workflows. It shouldn't be a routine just because the patient has PCOS. In non-male-factor infertility randomized and comparative evidence indicate no consistent live-birth advantage of ICSI over conventional IVF, and unnecessary ICSI is associated with added cost, manipulation of the laboratory and possibly imprinting related concerns with no clear advantage (Bhattacharya *et al*., 2001). In PCOS, the problem is not with the sperm entering but with the ooplasmic competence and endometrial timing.

The most important protocol development for PCOS is freeze-all with deferred FET. It can be used to remove the supraphysiologic endocrine environment of stimulation, to avoid late onset OHSS when combined with agonist trigger, and to transfer into a more controlled endometrium. The most important randomized trial in PCOS demonstrated a greater likelihood of live birth following frozen compared to fresh transfer and reduced rates of OHSS, with attention to pregnancy-related hypertensive outcomes (Chen *et al*., 2016). The FRESH trial and subsequent analyses confirm the overall concept that hyper-response populations should be treated with freeze-all, while indiscriminate freeze-all in unselected patients is not necessarily superior (Shi *et al*., 2018; Roque *et al*., 2019). The molecular rationale is summarized in Figure 5: Fresh transfer will give the embryo an advanced, inflamed, high-steroid endometrium, while deferred FET will achieve temporal alignment.

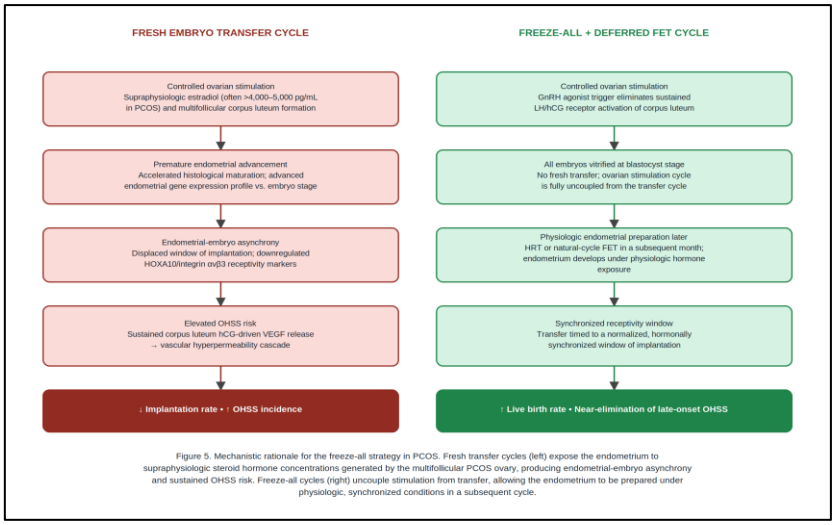



**Figure 5**: Mechanistic rationale for freeze-all in PCOS, contrasting fresh transfer during supraphysiologic ovarian stimulation with deferred FET after endocrine normalization.

The embryo stage is also important. Blastocyst culture enables better embryo selection and synchronisation with the FET scheduling, however in cases of unexpected poor developmental competence, the number of embryos may be reduced by extended culture. Although high yield

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of oocytes is associated with PCOS, laboratories should not only report the number of oocytes retrieved, but also the number of embryos that are usable after the blastocyst stage and the rate of fertilization. Vitrification has rendered freeze-all clinically viable because high survival rates of vitrified blastocysts are achievable in experienced laboratories; however, the viability of the blastocysts in different laboratories is an effect modifier and should be considered in outcome comparisons.

There is a need for some extra nuance in preparing for FET in PCOS. Natural-cycle FET is challenging in anovulatory patients, but attractive when ovulation is regular, as it maintains a corpus luteum that secretes progesterone, estradiol, relaxin, VEGF and vasoactive mediators involved in placentation. In chronic anovulation, artificial HRT-FET is logistically convenient and is sometimes required, but in certain ART populations, the absence of corpus-luteum has been linked to increased risk of preeclampsia and decreased vascular adaptation (Von Versen-Hoynck *et al*., 2019). Letrozole or modified natural ovulation may be a compromise for PCOS as it allows for the production of a corpus luteum, while still allowing for scheduling control; however, high quality trials specific to PCOS are still required.

The preparation of the endometrium should be tailored to each individual. Artificial cycles provide scheduling control and eliminate the hassle of trying to detect ovulation in the oligo-ovulatory PCOS; however, they are complex, need careful progesterone timing, and must be taken consistently. Letrozole-induced ovulatory FET may be especially appealing due to its potential to enhance the endometrial physiology, reduce estrogen exposure relative to stimulated cycles, and induce a corpus luteum. True natural cycle FET can only be used in patients who have predictable ovulation. The issue of whether or not FET is useful for PCOS is not in question, but what type of FET preparation gives the best chance of live birth with the least chance of miscarriage and hypertensive disease.

Hydrosalpinx, endometrial polyps, chronic endometritis, submucosal fibroids and intrauterine adhesions should be treated prior to embryo transfer as PCOS-specific receptivity impairment may occur in the presence of structural abnormalities. It is important to not fall into the trap of saying that all transfers that have failed are due to the biology of PCOS. A good ART pathway consists of a regular uterine assessment, a metabolic care tailored to the individual, a logical embryo transfer plan and the exclusion of unnecessary add-ons unless there is a clear indication for it.

## OUTCOMES: EFFICACY, SAFETY, AND CLINICAL INTERPRETATION

CLBR per initiated stimulation cycle is the most suitable primary endpoint for PCOS ART as a single retrieval may produce several embryos and multiple transfer opportunities. Pre-transfer pregnancy rates can be misleading as they do not account for cancelled cycles, OHSS prevention (freeze all), embryo banking or the cumulative effect of supernumerary embryos. In the presence of CLBR, PCOS patients can obtain similar or more favourable results as normo-ovulatory women of comparable age, as the increased number of oocytes is compensated by relatively small decreases in per-oocyte competence (Wang *et al*., 2022). Although age is the primary factor determining the risk and response for euploidy and live birth, BMI, hyperandrogenism, insulin resistance, AMH and stimulation intensity alter the risk and response.

Denominator and time horizon must be indicated in CLBR reporting. The following are not interchangeable: per started cycle, per oocyte retrieval episode, per embryo transfer episode, and per patient over multiple retrievals. Studies of PCOS should also include the number of embryos left after the first live birth, as well as the use of agonist trigger and whether or not subsequent births were counted. Failure to include these factors can make studies seem contradictory when they are actually measuring the different dimensions of reproductive opportunities.

Oocyte yield is characteristically elevated in PCOS, whereas the proportion of mature oocytes, fertilization rate, blastulation rate, and embryo utilization rate vary substantially across phenotypes and stimulation protocols. Consequently, the objective of ovarian stimulation in PCOS should be an optimal oocyte cohort rather than maximal retrieval. Excessive ovarian response is associated with elevated estradiol and progesterone concentrations, increased luteinized granulosa-cell mass, greater patient discomfort, and increased OHSS risk, without a corresponding improvement in live birth rate. This yield–competence paradox has direct implications for patient counselling: oocyte number is frequently

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equated with treatment success, yet intervening determinants — mature oocyte rate, fertilization rate, blastocyst conversion rate, embryo ploidy, uterine receptivity, and pregnancy-loss risk — collectively determine outcome. Oocyte quality should not be assumed to be compromised on the basis of PCOS diagnosis alone, since many PCOS patients achieve favourable cumulative outcomes despite baseline concerns regarding oocyte competence. Overall, PCOS confers a substantial embryo-yield advantage that requires disciplined protocol selection to translate safely into singleton live births.

There are many factors that contribute to a woman having a miscarriage with PCOS. These include hyperandrogenism, obesity, insulin resistance, impaired endometrial receptivity, chronic inflammation and possibly oocyte mitochondrial dysfunction. ART can minimize some failures by choosing embryos that are viable and by timing the transfer correctly, but cannot remove metabolic or uterine contributors. Higher rates of gestational diabetes, hypertensive disorders, preterm delivery, and neonatal complications have been reported in pregnancies complicated by PCOS, but the risk is confounded by BMI and metabolic disease (Boomsma *et al*., 2006; Sha *et al*., 2018). Preconception metabolic optimization and obstetric risk stratification thus continue to be a part of ART management.

Preimplantation genetic testing for aneuploidy (PGT-A) is a topic of debate in PCOS. Theoretically, the advantages are that the transfer of aneuploid embryos is reduced and that the time to pregnancy is shortened in patients who have numerous blastocysts. Limitations include cost, biopsy and vitrification requirements, difficulty interpreting mosaic results, and uncertain improvement in CLBR among younger patients. Patient preference, age, recurrent pregnancy loss, repeated implantation failure and embryo number are more relevant factors than PCOS alone.

The hallmark of safety in PCOS ART is OHSS. It has a core mediator, namely VEGF-A, in particular VEGF-A165, produced by luteinized granulosa cells in response to HCG and that acts through VEGFR2 to increase the endothelial permeability. In severe cases, third spacing, hemoconcentration and ascites, pleural effusion, thrombosis risk and renal compromise are produced downstream by Src, PI3K/AKT, nitric oxide, and vascular junctional pathways (Practice Committee of the American Society for Reproductive Medicine, 2016; Soares *et al*., 2008). High antral follicle count, elevated AMH, younger age, high peak estradiol, a large number of developing follicles, and a high number of oocytes retrieved are all associated with increased OHSS risk.

Early and late OHSS should be differentiated. Early OHSS is caused by luteotropic stimulation – either exogenous or endogenous – and develops after trigger and retrieval. Endogenous HCG (from an implanting pregnancy) is a major contributor to late OHSS, and thus freeze-all is the most effective way to prevent late OHSS. This is why in high-risk PCOS cycles, using agonist trigger only might lead to a decrease in early OHSS, but using freeze-all will help eliminate late severe OHSS. Intensive luteal rescue is required for fresh transfer after agonist trigger, and is not usually recommended in high-risk PCOS.

The contemporary OHSS-prevention package works very well: antagonist stimulation, low individualized gonadotropin dose, avoiding HCG trigger if possible, GnRH-agonist trigger, freeze-all, dopamine agonist prophylaxis in selected high-risk patients, and careful luteal management. In addition to agonist trigger and freeze-all, cabergoline decreases the VEGF-mediated permeability. Kisspeptin trigger is a physiologic alternative that stimulates endogenous GnRH/LH release and can help mitigate OHSS while promoting oocyte maturation, but is less well known than agonist trigger (Abbara *et al*., 2015).

Multiple pregnancy is no longer an inevitable ART complication, but instead a quality indicator. Historical PCOS risk included multifollicular ovulation induction, gonadotropin-IUI and multi-embryo transfer. The eSET technique, in modern IVF/FET, can lower the rate of twin pregnancy to about 1-2% and maintain the cumulative live birth rate with sequential transfer of cryopreserved embryos. For patients with PCOS, eSET is especially justifiable as they tend to create multiple blastocysts. Double embryo transfer should be unusual, personalised and based on age, embryo quality, failure of previous transfers and local policy.

The ethical justification for eSET is more compelling in PCOS than in other diagnoses, as the number of embryos available may be high. Although a twin pregnancy might seem to be efficient, it carries the risk of pre-term delivery, hypertensive disease, gestational diabetes, cesarean section, admission to the NICU, and

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long-term neonatal morbidity. Sequential singleton FET can help maintain family-building potential and minimise harm to mother and baby. Thus, multiple pregnancy should not be considered a success multiplier but rather an adverse outcome.

Neonatal and offspring considerations are important but should be taken with a grain of salt. PCOS is linked to maternal hyperinsulinemia, inflammation, androgen exposure, and obesity, which may impact fetal growth and subsequent metabolic risk. The variables added by ART are culture conditions, vitrification and endometrial preparation. At this time, there is no evidence to support withholding ART, but there is evidence to support minimizing supraphysiologic exposures, avoiding multiple pregnancy, selecting FET protocols that consider corpus luteum physiology, and incorporating long-term follow-up into future PCOS ART trials.

Other factors affecting modality choice are economic and psychosocial outcomes. IUI may be more economical in terms of cost per cycle, but less effective in terms of success after repeated failures; IVF can be more expensive initially, but can be more effective in terms of time to pregnancy and multiple embryo transfers from a single retrieval. Freeze-all increases delay and storage costs, but reduces severe OHSS and can help improve endometrial alignment. PCOS sufferers also have increased anxiety and depression and body-image issues, as well as increased treatment fatigue, which makes clear counseling and predictable protocols clinically relevant, not simply supportive.

## ADJUNCTIVE AND EMERGING STRATEGIES

Current most advanced adjunctive approach is individualized ovarian stimulation. AMH and AFC should not only be used to predict response, but also to delineate acceptable risk. Algorithms using AMH, AFC, age, BMI, basal FSH, previous response, and PCOS phenotype may help to minimise unnecessary response and gonadotropin administration. But these tools should be validated not only on the basis of the number of oocytes, but also on the basis of CLBR and OHSS. For PCOS, the model that recovers fewer oocytes but still allows for blastocysts production and avoids OHSS might be better.

Prediction models need to be integrated into clinical workflow. A helpful model would include the following: initiate FSH dose, timing of antagonist, frequency of monitoring, type of trigger, threshold for freeze-all, and OHSS prophylaxis, and adjust risk based on changes in follicle counts and estradiol. This is more beneficial than a one-off baseline calculator. Prediction tools, however, should not underestimate the need for treatment in obese or metabolically severe patients, where the pharmacokinetics of the serum gonadotropins and the sensitivity of the ovary may differ.

The biologic plausibility of co-administration of metformin during IVF/ICSI is related to AMPK activation, decreased hepatic glucose output, decreased insulin drive, and potential inhibition of granulosa-cell VEGF by mTOR/HIF-1-alpha pathways (Zhou *et al*., 2001). The results of meta-analyses indicate that antagonist/agonist-trigger/freeze-all cycles might show a smaller benefit due to the lower baseline risk, while in long-agonist cycles and insulin-resistant patients the benefit appears to be more pronounced, because the risk of OHSS is reduced (Palomba *et al*., 2013). There is some restoration of insulin second-messenger signaling and improvement in metabolic and follicular conditions with inositols, but there are formulation, dose, MI:DCI ratio and study quality differences.

They are of growing significance in obese insulin-resistant women with PCOS who are contemplating ART because they have the ability to decrease appetite, weight, insulin exposure and inflammation, which could lead to better ovulation, androgen levels and stimulation safety prior to IVF. They are commonly used ahead of time and have to be phased out carefully as there are not enough pregnancy safety data and most advice is to stop before getting pregnant. So their optimal use is not during stimulation or pregnancy, but rather in pre-ART metabolic conditioning.

Bariatric surgery is not a standard fertility treatment, but can be relevant for severe obesity with metabolic disease. It may help to enhance ovulation and the risk of pregnancy, but it is advisable to wait for the stabilization of weight and micronutrient status before trying to conceive. Bariatric referral should be tailored to the individual patient with PCOS, depending on BMI, comorbidity, age and ovarian reserve and should not be a blanket recommendation as delay may impact age-related reproductive potential in PCOS patients seeking ART.

Mechanistically, vitamin D, N-acetylcysteine, antioxidants, and anti-inflammatory adjuncts have

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some appeal, but have inconsistent clinical evidence.. Embryo and endometrial technologies, on the other hand, are moving forward at a fast pace. Time-lapse imaging, AI embryo-ranking systems and multimodal models (age, embryo morphology, morphokinetics, stimulation response, AMH, BMI, metabolic markers) can further enhance embryo ranking and risk prediction (Berntsen *et al*., 2022). A possible decision framework with AI assistance is presented in Figure 6. However, external validation, bias auditing, clear performance measures and evidence of live birth benefits are required for AI models, not just a reproduction of embryologist grading.

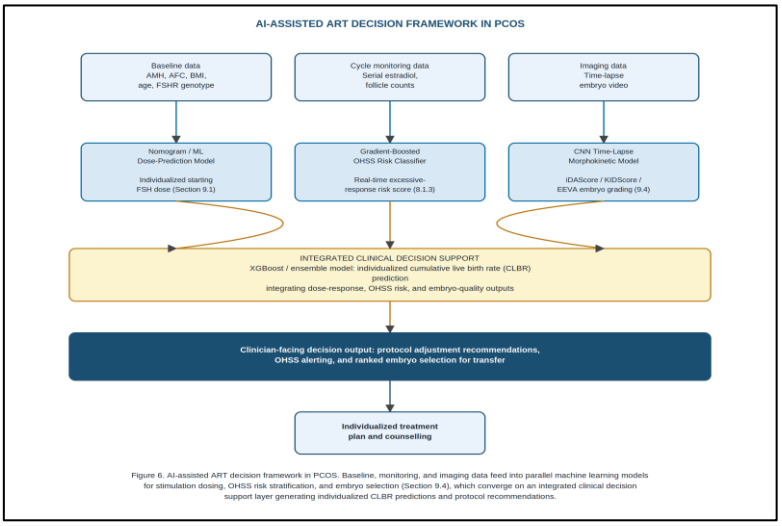



**Figure 6**: AI-assisted ART decision framework in PCOS, integrating baseline data, cycle monitoring, embryo imaging, molecular assays, and clinical outcomes to support individualized treatment planning.

The potential of AI in PCOS should go beyond embryo selection. Models could be used to predict OHSS, to suggest a safer level of stimulation, to identify patients who might benefit from freeze-all, to choose FET preparation and to estimate obstetric risk. The best systems will combine imaging, endocrine/metabolic, genetic, and clinical information. The lowest will just repack morphology scores. AI systems must be shown to be transferable between laboratories, ethnic groups, BMI ranges, and PCOS phenotypes before they can be used routinely, and should be demonstrated using calibration plots and decision-curve analysis, not just accuracy.

Use of endometrial receptivity assays, microbiome profiling and transcriptomic tests should be limited. The target population is a plausible one, given that the presence of a progesterone-resistant endometrium and inflammatory dysregulation are biologically plausible; however, routine testing of receptivity has not led to a consistent increase in live birth in unselected IVF populations. Future PCOS-specific trials should evaluate the potential of molecular endometrial profiling to select patients that can benefit from modified natural FET, alteration of the progesterone duration, anti-inflammatory treatment, or correction of the microbiome.

## COMPARATIVE CLINICAL FRAMEWORK

Pragmatically, the role of ART modalities in PCOS can be summarized. Letrozole-IUI is suitable for young patients with patent tubes, mild infertility duration, good semen parameters and low multiple-follicle risk. IVF is preferred if oral therapy or IUI has failed, if there is a diminished time for stepwise care due to tubal disease or age, and if a higher per-cycle success rate is required. Sperm or fertilization factors are an indication of ICSI, not of PCOS. The use of freeze-all plus FET is preferred when there is high estradiol, large number of follicles, or asynchrony of the endometrium, or when there is a risk of OHSS. The eSET policy of freeze-all and sequential FET maintains CLBR and reduces multiple pregnancy risk. A comparative summary of modalities, indications, advantages, risks, and evidence base has been retained and is summarized in Table 1.

**Table 1:** Comparative summary of ART modalities in PCOS-associated infertility

| **Parameter** | **IUI** | **Conventional** | **ICSI** | **FET (from** | **Freeze-all +** |
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| | | **IVF** | | **prior fresh cycle)** | **FET** |
|---|---|---|---|---|---|
| Primary indications | Mild male factor; OI failure with patent tubes; first ART step in appropriately selected patients | OI failure with tubal patency and adequate semen parameters; multiple prior IUI failures | Moderate–severe male factor; prior fertilization failure; PGT-A cycles | Surplus cryopreserved embryos following a prior fresh stimulation cycle | Elevated OHSS risk (AFC >24, AMH >3.4 ng/mL); compromised endometrium during COS; universal recommended PCOS standard |
| CLBR per episode | 15–25% cumulative over 3–6 cycles | 35–55% per started cycle (age- and protocol-dependent) | Comparable to IVF in non-male-factor PCOS (30–50%) | Dependent on cryopreserved embryo cohort quality; cumulative across sequential transfers | Comparable to, or exceeding, fresh transfer CLBR in PCOS; 49.3% vs. 42.5% per first transfer in the pivotal RCT |
| OHSS risk | Low (mono/bi-follicular letrozole-based stimulation) | Moderate–high without antagonist/agonist-trigger mitigation | Moderate–high (shares COS risk profile with IVF) | Minimal (no fresh ovarian stimulation in the transfer cycle) | Minimal (agonist trigger eliminates late-onset OHSS) |
| Multiple pregnancy risk | 8–15% with gonadotropin-stimulated IUI; lower with letrozole | Historically 20–30% with multi-embryo transfer; 1–2% with eSET | Same as IVF under eSET policy | 1–2% under eSET; slightly elevated monozygotic twinning (1.0–2.5%) with vitrification | Same as eSET-policy FET |
| Key advantage | Least invasive; lowest cost; minimal monitoring burden | Highest absolute per-cycle success among first-line ART options | Overcomes fertilization failure; necessary for PGT-A workflows | Utilizes existing cryopreserved embryo cohort without repeat stimulation | Optimal endometrial receptivity; eliminates COS-endometrial asynchrony; lowest OHSS incidence |
| Key limitation | Lower per-cycle efficacy than IVF; plateau effect beyond 4 cycles | OHSS risk without protocol modification; higher cost than IUI | No demonstrated benefit over IVF in non-male-factor PCOS; theoretical epigenetic/imprinting concerns | Contingent on prior fresh cycle yield and embryo quality | Elevated preeclampsia risk in HRT-FET cycles lacking a corpus |

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| | | | | | |
|---|---|---|---|---|---|
| | | | | | luteum; requires deferred-transfer counselling |
| Representative evidence base | Cohlen *et al*. (2018) | Heijnen *et al*. (2006); Bosch *et al*. (2020) | Bhattacharya *et al*. (2001) | Maheshwari *et al*. (2011) | Chen *et al*. (2016); Shi *et al*. (2018); Roque *et al*. (2019) |

There are only three scenarios to consider when making decisions. Letrozole induction followed by timed intercourse or IUI is effective in low risk young PCOS when tubes are patent and semen is normal, prior to IVF. If the patient has intermediate risk PCOS and failed to conceive with oral agents, or is at risk of age-related pregnancy loss, or had multiple IUI failures, IVF using antagonist stimulation and planned eSET is preferred. For high-risk PCOS with very high AMH/AFC, previous OHSS, high estradiol, and anticipated high number of oocytes, antagonist stimulation, agonist trigger, freeze-all, and deferred FET should be considered from the beginning and not be a last-resort option once an excessive response has been achieved.

The second decision layer is related to embryo transfer. Fresh transfer may be acceptable only if response is moderate, if there is no increase in progesterone, if there has been no excessive exposure to estradiol, if the patient is asymptomatic, if there is a low risk of OHSS and if the endometrium is appropriate. This is preferable if any of these conditions is not met, and can be deferred. In reality, many PCOS patients are in the category of deferred transfer, not because it is not an effective concept in theory but because the safety and synchrony benefits of FET are clinically relevant.

## FUTURE PERSPECTIVES

Syndrome-level stratification should be replaced with phenotype-level and molecule-level stratification in the next phase of PCOS ART. Multi-omics analysis of FF, cumulus, granulosa, endometrium and serum could identify signatures of oocyte competence, hyper-response, lack of implantation and miscarriage. Mitochondrial medicine is another priority since ATP production in the oocyte, spindle integrity, oxidative injury and embryo metabolism are possible factors affecting the yield-competence paradox. Effective interventions like CoQ10 or specific antioxidants require live birth trials.

Baseline AMH/AFC would be paired with androgen profile, insulin-resistance markers, inflammatory markers, follicular fluid metabolites, cumulus-cell transcriptomics and endometrial receptivity markers in a high-priority biomarker panel. Such a panel should not be created to diagnose but to allocate treatment – low dose stimulation versus conventional stimulation, fresh eligibility versus mandatory freeze all, natural FET versus letrozole-FET, and metabolic preconditioning or not. Without changing care decisions, biomarkers are unlikely to improve care.

Uterine microbiome and immune profiling could be useful in the future for identifying patients with PCOS with inflammatory-dysbiotic implantation failure, although contamination by low-biomass, variability in sequencing pipelines and uncertainty about treatment thresholds hinder translation at this time (Moreno *et al*., 2016). Organoid and three dimensional culture systems can be used to model the endometrium in PCOS, granulosa-cell steroidogenesis, and drug responses, thus allowing an 'in between' link between the findings from a clinical trial and the molecular findings from an observation study. Gene editing is not yet a therapeutic approach and is only a research tool due to the polygenetic nature of PCOS, its pleiotropic nature, and the unethical nature of embryo editing. Fertility preservation should be investigated in patients who are undergoing gonadotoxic therapy or who are planning for delayed childbearing; however, PCOS should not be assumed to be a benign high-reserve condition and the number, competence, metabolic state, and age of the oocytes are still the most important factors.

This should affect the design of trials. Future studies should include the Rotterdam phenotype, the androgen status, insulin resistance, BMI, AMH, AFC, stimulation dose, trigger type, luteal

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support, transfer stage, embryo number, FET preparation, corpus luteum status, CLBR, OHSS, miscarriage, hypertensive disorders, gestational diabetes, birth weight, and neonatal outcomes. If this is not there, the field will keep on producing averages that are safe for no patient.

Equity needs to be considered in future research. The prevalence of PCOS, the presentation of the phenotype, the distribution of BMI, access to ART, affordability of freeze-all and availability of antagonist protocols varies significantly between health systems. The protocol used in a well monitored private IVF clinic may not be possible in a low resource clinic. On the other hand, inexpensive measures like letrozole, judicious cancellation policies, and eSET can significantly minimize damage.

## LIMITATIONS

Several limitations of this review warrant acknowledgment. First, as a structured narrative review rather than a formal meta-analysis, the primary analytical approach is qualitative synthesis, which is inherently more susceptible to interpretive bias than quantitative pooling. Second, substantial heterogeneity in PCOS diagnostic criteria, phenotype distribution, stimulation protocols, trigger types, embryo transfer strategies, and outcome definitions across included studies precluded meta-analytic pooling for most outcomes and limited direct comparability. Third, the lower date boundary of January 2000 may have excluded early evidence predating the Rotterdam consensus. Fourth, despite no language restriction, studies for which full-text translations were unobtainable were excluded, potentially introducing language bias. Fifth, the quality of included studies varied considerably; observational designs predominate in several outcome domains, limiting causal inference. Sixth, publication bias cannot be excluded, as trials reporting neutral or negative outcomes may be underrepresented in the published literature. These limitations should be considered when interpreting the evidence statements and clinical recommendations presented in this review.

## CONCLUSION

ART can be highly successful in treating PCOS-associated infertility when treatment is tailored to the molecular and clinical features of the syndrome. The underlying reproductive failure is not caused by anovulation alone, but reflects a complex combination of abnormalities in androgen biosynthesis, dysregulated insulin signaling, AMH-mediated follicular arrest, defective oocyte bioenergetics, and impaired endometrial receptivity. Notably, the same biological substrate that gives PCOS patients their high cumulative reproductive potential is also responsible for the major risks associated with ART, namely OHSS and endometrial–embryonic asynchrony. Current best practice therefore centers on individualized antagonist-protocol stimulation, conservative gonadotropin dosing, agonist triggering in high responders, freeze-all strategies in high-risk patients, deferred frozen embryo transfer with careful attention to corpus luteum physiology, and elective single embryo transfer. With proper implementation, this approach can achieve cumulative live birth rates in PCOS comparable to those in normo-ovulatory patients, with minimal avoidable harm. The remaining challenge is one of precision: determining which metabolic, endometrial, artificial intelligence–based, and omics-guided adjuncts offer a meaningful improvement in live birth rate, rather than merely a surrogate indicator of treatment response.

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