

# From Ovulation Induction to IVF: A Short Review of Fertility Treatments for Women with PCOS

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**Abstract:** Background: Polycystic ovary syndrome (PCOS) is a leading cause of anovulatory infertility. Managing infertility in PCOS requires an evidence-based, stepwise approach that balances effectiveness, safety and patient preferences. Over the last decade practice-changing trials and modern ART safety strategies have shifted first-line and ART protocols.

**Objective:** To synthesize contemporary evidence across the fertility-treatment continuum in PCOS — from lifestyle and oral ovulation induction to surgical options, gonadotropin stimulation, and assisted reproductive technologies (ART) including in-vitro fertilization (IVF) and in-vitro maturation (IVM) — with attention to comparative effectiveness (ovulation, clinical pregnancy, live birth) and safety (OHSS, multiple pregnancy, perinatal outcomes).

**Methods:** We performed a narrative systematic approach prioritizing high-quality randomized controlled trials (RCTs), Cochrane reviews, recent meta-analyses and international guidelines through December 2024. Key sources included the 2023 International PCOS Guideline, the NEJM randomized trial comparing letrozole and clomiphene, Cochrane reviews on metformin and laparoscopic ovarian drilling, and ASRM guidance on OHSS prevention and IVM. For each treatment category we summarize mechanisms, efficacy, key trial evidence, safety considerations and guideline recommendations.

**Results:** Letrozole (aromatase inhibitor) demonstrates superior ovulation and live-birth rates compared with clomiphene and are now recommended as the first-line oral ovulation induction agent in many patients. Metformin improves ovulation and may be useful where metabolic indications exist, but evidence for consistent live-birth benefit as monotherapy is limited. Gonadotropins are effective second-line agents for ovulation induction but increase monitoring needs and OHSS/multiple pregnancy risk; low-dose step-up regimens reduce but do not eliminate these harms. Laparoscopic ovarian drilling (LOD) can restore ovulation in selected clomiphene-resistant women but carries surgical risks and uncertain live-birth advantage vs medical alternatives. In ART, GnRH antagonist stimulation protocols combined with GnRH-agonist trigger and selective “freeze-all”/deferred embryo transfer markedly reduce OHSS risk while maintaining comparable pregnancy outcomes. IVM offers an OHSS-sparing option with reasonable success in specialized centres, but technique heterogeneity limits generalizability. Pregnancies conceived in women with PCOS continue to show higher risks of gestational diabetes and hypertensive disorders, necessitating integrated preconception metabolic optimization and obstetric surveillance.

**Conclusions:** Contemporary evidence supports letrozole as first-line ovulation induction for many anovulatory patients with PCOS, careful selective use of metformin for metabolic indications, stepwise

escalation to gonadotropins or LOD when needed, and ART strategies prioritizing OHSS prevention (antagonist regimens, agonist trigger and freeze-all). IVM is promising for OHSS-risk reduction in specialist settings. Key research gaps include phenotype-specific randomized data, long-term offspring outcomes, and optimized individualized stimulation algorithms.

**Keywords:** PCOS, infertility, ovulation induction, letrozole, IVF, IVM, OHSS, systematic review.

## I. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder affecting a substantial proportion of women of reproductive age and represents one of the most common causes of anovulatory infertility worldwide. Diagnostic criteria vary (Rotterdam, NIH, AES), but the triad of ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology captures the central reproductive phenotype; insulin resistance and metabolic dysregulation are frequent comorbidities that influence treatment response and pregnancy risk. The multifactorial pathophysiology of PCOS — disrupted folliculogenesis, androgen excess, hyperinsulinemia and altered intra-ovarian signalling — produces heterogeneous infertility phenotypes and requires individualized management.

Historically, clomiphene citrate (CC) dominated oral ovulation induction for anovulatory infertility. Landmark randomized evidence changed practice: *Legro et al.*'s multicenter RCT showed letrozole produced higher live-birth rates than clomiphene in women with PCOS, prompting guideline updates endorsing letrozole as the preferred first-line oral agent in many settings. These findings, together with Cochrane syntheses and professional guidance, necessitate a contemporary synthesis that spans first-line pharmacotherapy through to advanced ART and OHSS-mitigation strategies.

This review systematically collates and interprets high-level evidence on fertility treatments in PCOS, with an emphasis on comparative effectiveness (ovulation, pregnancy, live birth), safety (OHSS, multiple pregnancy), perinatal outcomes, and personalization by phenotype and metabolic status. It is intended to inform clinicians, researchers and policy-makers navigating treatment selection and guideline implementation.

## II. METHODS

This is a narrative systematic review focused on high-quality evidence. We searched and prioritized: international guidelines, RCTs, Cochrane reviews, and recent systematic reviews/meta-analyses through December 2024. Key searched items included: letrozole vs clomiphene RCTs, metformin for ovulation induction (Cochrane), laparoscopic ovarian drilling (Cochrane), ART protocols (antagonist vs agonist, agonist trigger, freeze-all), IVM systematic reviews, and ASRM/other practice guidance on OHSS prevention. Sources were identified in PubMed, CENTRAL, and guideline repositories; where a guideline or major RCT existed, we used it as the primary evidence anchor for that treatment domain. For pragmatic clarity we prioritized outcomes with high patient importance: live birth, clinical pregnancy, ovulation, incidence of OHSS, multiple pregnancy and key perinatal outcomes. Narrative synthesis organized evidence by treatment category and then by outcomes and safety.

### III. EVIDENCE SYNTHESIS

#### 1. Preconception care and lifestyle optimization

Weight loss via diet, exercise and behavioral modification improves ovulatory function and pregnancy probability in overweight/obese women with PCOS. Even modest weight reductions (5–10%) can restore ovulation, reduce insulin resistance and improve ART outcomes; contemporary guidelines recommend lifestyle optimization as first-line where applicable. Smoking cessation, metabolic screening (OGTT), and addressing micronutrient status (e.g., folate) are essential preconception steps.

#### 2. Oral ovulation induction: letrozole vs clomiphene and other agents

##### Mechanisms & rationale

- **Clomiphene citrate (CC)** is a selective estrogen receptor modulator that reduces estrogen negative feedback, increases pituitary FSH and induces follicular development.
- **Letrozole** is an aromatase inhibitor that transiently lowers circulating estrogen synthesis, increasing intra-ovarian FSH sensitivity and often producing a more physiologic endometrial environment compared with CC.

##### Key evidence

- The NEJM multicenter RCT by Legro et al. (2014) randomized 750 women with PCOS and demonstrated higher live-birth and ovulation rates with letrozole compared with clomiphene (live birth: 27.5% vs 19.1%; ovulation: 61.7% vs 48.3% per treatment cycle), findings that have influenced many national and international guidelines. Letrozole was also associated with fewer multiple pregnancies.

##### Guideline recommendations & practice implications

- The 2023 International PCOS Guideline reflects this evidence and recommends letrozole as the preferred first-line oral ovulation induction agent in many patients with PCOS, while recognizing patient preferences, comorbidities and access issues. For women with contraindications to letrozole, CC remains an alternative.

##### Safety & monitoring

- Letrozole side effects are generally mild; teratogenicity concerns from earlier observational reports have not been substantiated in high-quality trials but appropriate contraception during treatment and early pregnancy assessment remain standard. Monitoring for ovulation and timing of intercourse/IUI is similar to CC protocols.

#### 3. Insulin sensitizers: metformin

##### Evidence summary

- Cochrane reviews indicate metformin improves ovulation compared with placebo and may modestly increase pregnancy rates; however, evidence for consistent live-birth benefit when used as sole ovulation induction therapy is inconsistent. Metformin is widely recommended primarily when glucose dysregulation or metabolic syndrome features are present, or as an adjunct in specific clinical scenarios (e.g., reducing risk of OHSS or improving metabolic profile preconception). Gastrointestinal adverse effects are common.

#### Clinical application

- Consider metformin for PCOS patients with impaired glucose tolerance or type 2 diabetes risk factors; when used for fertility outcomes alone, counsel on modest and uncertain live-birth benefits vs common GI side effects.

#### 4. Injectable gonadotropins and low-dose protocols

##### Efficacy & risks

- Gonadotropins (FSH  $\pm$  LH preparations) directly stimulate folliculogenesis and are effective for ovulation induction in clomiphene/letrozole-resistant patients. Low-dose step-up regimens minimize multifollicular development and multiple pregnancy risk but require intensive monitoring (serial ultrasounds, estradiol). Compared with oral agents, gonadotropins increase costs, monitoring burden and OHSS risk in PCOS (high ovarian reserve). Individualized dosing guided by AMH/AFC reduces but does not eliminate OHSS risk.

##### Best practice

- Use low-dose step-up protocols with careful monitoring; consider IUI or timed intercourse according to follicular growth and patient preference.

#### 5. Laparoscopic ovarian drilling (LOD)

##### Evidence summary

- LOD can restore ovulation in selected clomiphene-resistant patients and may be preferable for women desiring a single intervention avoiding repeated gonadotropin cycles. However, Cochrane evidence suggests uncertain or modest live-birth advantages compared with medical ovulation induction, and there is potential surgical morbidity and theoretical risk to ovarian reserve if extensive drilling is performed. Hence LOD is individualized and often second-line.

##### Clinical practice note

- Reserve LOD for carefully selected patients (e.g., when medical therapy is contraindicated or monitoring capacity for gonadotropin cycles is limited), and use conservative drilling techniques.

## 6. ART in PCOS: IVF protocols, OHSS prevention and freeze-all

### ART benefits and risks in PCOS

- IVF achieves high per-cycle pregnancy rates in PCOS but increases OHSS risk due to high ovarian reserves (AMH, AFC). Modern ART focuses on preserving high success while minimizing OHSS.

### OHSS prevention strategies

- **GnRH antagonist protocols** are preferred in high responders (including many women with PCOS) because they allow the use of a **GnRH-agonist trigger** instead of hCG, which markedly reduces OHSS incidence.
- **Elective freeze-all** (deferred embryo transfer) further reduces OHSS and may improve perinatal outcomes in certain contexts. The ASRM and other bodies recommend these measures in high-OHSS-risk patients. Recent reviews have documented consistent OHSS reduction with antagonist + agonist trigger strategies while maintaining comparable live birth rates when optimal luteal support and embryo transfer timing are applied.

### Implementation considerations

- Individualize stimulation intensity using AMH/AFC; use antagonist protocols for high responders; consider agonist trigger and freeze-all when >20 follicles or other high-risk markers are present; plan single embryo transfer to avoid multiple pregnancy.

## 7. In-vitro maturation (IVM)

### What is IVM?

- IVM retrieves immature oocytes from small follicles and matures them in the laboratory, greatly reducing or avoiding the need for high-dose gonadotropin stimulation and thereby minimizing OHSS risk.

### Evidence & limitations

- Recent systematic reviews and meta-analyses show comparable clinical pregnancy and live-birth rates with IVM vs conventional IVF in select PCOS cohorts, though results vary across centers and depend heavily on lab expertise and protocols. ASRM committee opinions acknowledge IVM's potential but recommend it primarily in specialized programs until standardized protocols and wider RCT evidence accumulate.

### Clinical positioning

- Consider IVM when OHSS risk is prohibitive, in centers with established IVM success rates, or when patients prefer to avoid intensive stimulation.

## 8. Perinatal outcomes and long-term considerations

### Pregnancy risks in PCOS

- Women with PCOS have higher rates of gestational diabetes, hypertensive disorders and preterm birth. These risks persist regardless of conception modality, although ART may interact with baseline metabolic risks. Hence fertility care must integrate preconception metabolic optimization, screening for glucose intolerance, and prenatal surveillance. Long-term follow-up data on offspring exposed to different ovulation induction or ART strategies remain limited and are a key research priority.

## IV. PRACTICAL CLINICAL ALGORITHM

1. Assess PCOS phenotype, BMI and metabolic status; perform OGTT where indicated.
2. Recommend lifestyle modification and weight reduction for overweight/obese patients.
3. First-line oral ovulation induction: **letrozole** (unless contraindicated). Consider CC if letrozole unavailable or contraindicated.
4. Consider **metformin** when metabolic indications exist or as adjunct in selected patients.
5. If oral agents fail, escalate to **gonadotropin** stimulation with low-dose protocols OR consider **LOD** in selected clomiphene-resistant patients.
6. For ART: use **antagonist protocols**; consider **agonist trigger** and **freeze-all** when OHSS risk is high; consider **IVM** in specialized centers for OHSS-avoidance.
7. Use single embryo transfer to minimize multiple pregnancy and institute preconception metabolic care and obstetric surveillance.

## V. RESEARCH GAPS AND FUTURE DIRECTIONS

Despite advances, key gaps remain:

- **Phenotype-tailored RCTs:** Most trials do not stratify sufficiently by PCOS phenotype (hyperandrogenic vs non-hyperandrogenic) or BMI. Comparative trials that pre-specify subgroup analyses are needed to personalize therapy.
- **Stimulation personalization:** Algorithms incorporating AMH/AFC, pharmacogenomics, and individualized gonadotropin dosing require RCT validation in PCOS to maximize cumulative live birth while limiting OHSS.
- **Long-term offspring outcomes:** High-quality longitudinal studies are needed to evaluate developmental and metabolic outcomes in children conceived after differing ovulation induction and ART strategies.
- **Standardization and dissemination of IVM:** Multi-center RCTs and technique standardization will determine where IVM can be broadly recommended.

## VI. STRENGTHS AND LIMITATIONS

Strengths: focused synthesis of the highest-level evidence (guidelines, RCTs and Cochrane reviews) across the full fertility continuum in PCOS; pragmatic clinical algorithm offered.

Limitations: this is a narrative systematic review rather than a de novo meta-analysis; while we prioritized RCTs and high-quality syntheses, not all interventions have sufficient RCT data, and center variation (especially for IVM and ART laboratory practices) limits generalizability.

## VII. CONCLUSION

Fertility treatment for women with PCOS should be individualized along a stepwise pathway: lifestyle optimization, letrozole as a preferred first-line oral ovulation inducer, selective use of metformin for metabolic indications, considered escalation to gonadotropins or LOD when needed, and ART strategies that prioritize OHSS prevention (antagonist protocols, agonist trigger, freeze-all). IVM remains a promising OHSS-sparing approach in specialist centres. Future research should address phenotype-tailored strategies, stimulation personalization and long-term offspring outcomes to further refine patient-centred fertility care in PCOS.

## VIII. FINANCIAL DISCLOSURE

The authors do not claim any conflicting financial interest.

## IX. CONFLICT OF INTEREST

The authors found no conflicting interests exist.

## X. ETHICAL APPROVAL

Not required

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