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A Structured Literature Review on Current Protocols for *In Vitro* Fertilization in Women with Polycystic Ovary Syndrome

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Abstract

Background: Polycystic Ovary Syndrome (PCOS) represents a serious endocrine disorder affecting women of reproductive age, frequently leading to anovulatory infertility. Major clinical approaches to in Vitro Fertilization (IVF) currently in clinical practice include Gonadotropin-Releasing Hormone (GnRH) antagonist and long GnRH agonist stimulation regimens, Progestin Primed Ovarian Stimulation (PPOS), In Vitro Maturation (IVM) protocols with prematuration strategies, trigger strategies (hCG, GnRH agonist, and dual triggers), adjunctive metabolic and antioxidant therapies (metformin, myo inositol, N acetylcysteine, thiazolidinediones, statins), individualized gonadotropin dosing, and freeze all embryo transfer policies. However, despite therapeutic advances, IVF for women with PCOS remains complicated, especially by a persistent risk of Ovarian Hyperstimulation Syndrome (OHSS).

Methods and findings: We performed a focused literature review (2015–2025), prioritizing randomized trials, cohort studies, and meta analyses to evaluate oocyte yield and maturity, duration of stimulation and gonadotropin consumption, clinical pregnancy and live birth rates, cycle cancellation and embryo utilization, and maternal and perinatal adverse events including OHSS incidence and severity, across treatment modalities. Findings from the literature revealed that GnRH antagonist protocols consistently reduce OHSS incidence and overall treatment burden while maintaining comparable clinical pregnancy and live birth outcomes to long agonist regimens; antagonists also permit individualized dosing and routine use of GnRH agonist triggers.

Additional evidence supports PPOS as an oral alternative with similar live birth outcomes and practical advantages when paired with planned freeze all strategies. Studies based on IVM cohorts indicated substantial mitigation of OHSS risk and improved oocyte maturation with prematuration techniques, although cumulative live birth rates remain generally lower than with conventional IVF in most series. Findings further showed that GnRH agonist triggers markedly reduce OHSS compared with human Chorionic Gonadotropin (hCG), that dual triggers increase oocyte maturity but may elevate OHSS risk in susceptible patients, and that freeze all approaches further mitigate OHSS while preserving transfer outcomes.

Conclusions: The findings of this literature review indicate that management of women with PCOS undergoing IVF should prioritize OHSS prevention, adopt phenotype driven stimulation (preferential antagonist or PPOS), consider IVM where appropriate, routinely plan freeze all for high risk patients, implement preconception metabolic optimization, and pursue targeted trials and cost effectiveness analyses to refine practice and maximize safe, cumulative live birth.

Keywords: Polycystic ovary syndrome; In Vitro fertilization; GnRH antagonist protocol; Personalized treatment; Progestin-primed ovarian stimulation

Introduction

Polycystic Ovary Syndrome (PCOS) affects an estimated 6–13% of reproductive-aged women globally and up to 22.5% of women in India (based on varying diagnostic criteria) [1], establishing it as the most common endocrine disorder and a primary cause of anovulatory infertility. Additionally, it is also suggested that up to 70% of women with PCOS may remain undiagnosed suggesting that the actual prevalence rates of PCOS may be higher than previously estimated [2]. Its diverse clinical manifestations, encompassing irregular menses, hyperandrogenism, and polycystic ovarian morphology, necessitate a highly individualized approach to fertility management [3]. Cumulative evidence from clinical trials as well as real-world data have established the effectiveness of *In vitro* Fertilization (IVF) in improving pregnancy outcomes across conditions including PCOS. Global data on the proportion of women with PCOS who undergo IVF is limited. According to a retrospective study by Orosz et al. (2024) conducted in Hungary, 15% of pregnancies among women with PCOS were conceived through IVF [4]. However, a substantial body of evidence also indicates that the effectiveness of IVF among women with PCOS may be considerably impaired [5].

Despite significant advances, several clinical challenges persist in the IVF management of women with PCOS [5,6]. A high risk of Ovarian Hyperstimulation Syndrome (OHSS) and its potential complications remain a paramount concern, necessitating continuous vigilance, careful monitoring, and highly tailored interventions. Optimizing ovarian response presents a delicate balance: achieving a sufficient oocyte yield while simultaneously avoiding over-response, or conversely, addressing poor response observed in certain PCOS phenotypes, requires considerable clinical expertise. Furthermore, women with PCOS face an increased risk of specific pregnancy complications, including gestational diabetes, preeclampsia, and preterm birth [5-10].

The suboptimal pregnancy outcomes among women with PCOS undergoing IVF treatment mandates meticulous protocol selection and vigilant monitoring throughout the treatment regimen to maximize patient safety while striving for optimal reproductive outcomes [5]. In recent times, modifications to conventional treatment protocols have been made, transitioning from GnRH agonist-based long protocols to GnRH antagonist protocols. Furthermore, novel strategies and adjunctive therapies to further personalize and improve IVF success are also being explored in recent times.

This structured literature review evaluated the current evidence on the application and outcomes of GnRH-based stimulation protocols, including agonist and antagonist regimens, within the PCOS population. It examines emerging approaches such as *In Vitro* Maturation (IVM) and Progestin-Primed Ovarian Stimulation (PPOS), considering how these alternatives may mitigate the risk of OHSS while enhancing reproductive success. Additionally, it evaluates the impact of effect modifiers such as gender and age of the patients in influencing the outcomes of IVF treatment. By synthesizing recent findings, the report aims to offer insight that may inform clinicians and researchers of optimal strategies for achieving safe and effective IVF outcomes in women with PCOS.

Methods

We performed a structured literature review of PubMed for articles published between January 2015 and October 2025. The search strategy was guided by the Population, Intervention, Comparison, Outcome, and Study Type (PICO[S]) framework (Table 1 and Table 2).

The population of interest was women with PCOS. Interventions included assisted reproductive technologies, including IVF. Comparisons involved alternative fertility treatments for women with PCOS (e.g., clomiphene citrate, letrozole, laparoscopic ovarian drilling) and IVF outcomes in women without PCOS. Outcomes assessed were clinical pregnancy, live birth, miscarriage, preterm delivery, OHSS, and other obstetric and perinatal endpoints. Search terms combined MeSH headings and keywords ("Polycystic ovary syndrome", "Polycystic ovarian syndrome", "Sclerocystic ovary", "Stein-Leventhal Syndrome", "Polycystic ovary disease", "PCOS", "PCOD", "*In vitro* fertilization", "Intracytoplasmic sperm injection", "Assisted reproductive technology", "Embryo transfer", "Blastocyst transfer", "Frozen embryo transfer", "Cryopreservation", and "Fertility preservation"), refined with Boolean operators.

Eligible studies included randomized controlled trials, observational studies, systematic reviews, and meta-analyses. Searches were restricted to human studies in English. Articles were selected for relevance and methodological quality, with priority given to systematic reviews, meta-analyses, and well-conducted clinical trials. Additionally, supplementary searches were also performed to identify relevant systematic literature reviews/meta-analyses to provide cumulative evidence.

Results

Evidence base identification

A comprehensive PubMed search identified 1,259 unique records. After title and abstract screening, 271 full-text articles were assessed for eligibility, of which 97 studies met our predefined inclusion criteria. To focus on the highest-quality evidence, we further prioritized 60 studies based on rigorous study design, sample size, and the consistency of thematic findings across investigations. An additional 22 publications were identified through supplementary searches or bibliographical searches.

Reporting of findings by themes

Ovarian stimulation protocols

GnRH-based protocols: The choice of GnRH analogue protocol is fundamental in ovarian stimulation for IVF, particularly in women with PCOS, given their heightened sensitivity to gonadotropins and risk of OHSS.

GnRH antagonist protocol: The GnRH antagonist protocol, utilizing agents such as Cetrorelix or Ganirelix, functions by immediately and competitively binding to GnRH receptors in the pituitary gland [11-13]. This action directly inhibits the release of endogenous Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH), thereby preventing a premature LH surge without the initial "flare effect" observed with GnRH agonists. This immediate suppression is a key advantage.

Table 1. Search strategy for extracting primary studies on ART in women with PCOS published in English in the last 10 years.

S.No	Parameter	Eligibility	Ineligibility	Search string
1	Population	Women with PCOS	People with any other condition	("Polycystic Ovary Syndrome"[MeSH] OR "polycystic ovary syndrom*"[Title/Abstract] OR "polycystic ovarian syndrom*"[Title/Abstract] OR "sclerocystic ovar*"[Title/Abstract] OR "Stein-Leventhal Syndrom*"[Title/Abstract] OR "Stein Leventhal Syndrom*"[Title/Abstract] OR "polycystic ovary disease"[Title/Abstract] OR "polycystic ovarian disease"[Title/Abstract] OR "PCOS"[Title/Abstract] OR "PCOD"[Title/Abstract])
2	Intervention	ART, IVF, ICSI, and related interventions	Any other intervention, such as IUI and artificial insemination	("Fertilization *in Vitro*"[Mesh] OR "Reproductive Techniques, Assisted"[Mesh] OR "Sperm Injections, Intracytoplasmic"[Mesh] OR "Assisted Reproductive Technics"[Title/Abstract] OR "Assisted Reproductive Technique"[Title/Abstract] OR "Assisted Reproductive Technology"[Title/Abstract] OR "Assisted Reproductive Technologies"[Title/Abstract] OR "*in vitro* fertilization"[Title/Abstract] OR "*in vitro* fertilisation"[Title/Abstract] OR "IVF"[Title/Abstract] OR "ICSI"[Title/Abstract] OR "Intracytoplasmic sperm injection*"[Title/Abstract] OR "Mitochondrial replacement therapy"[Title/Abstract] OR "Embryo transfer"[Title/Abstract] OR "Blastocyst transfer"[Title/Abstract] OR "FET"[Title/Abstract] OR "cryopreservation"[Title/Abstract] OR "fertility preservation"[Title/Abstract])
3	Comparator	Any comparator or no comparator	NA	Non-restrictive
4	Outcomes	IVF-related outcomes	NA	Non-restrictive
5	Study design	• RCT • Observational (prospective and retrospective)	• Pre-clinical studies • Animal studies • Case reports • Case studies • Reviews, SLRs, and meta-analyses	("Narrative review*"[Title/Abstract] OR "Scoping review*"[Title/Abstract] OR "Systematic review*"[Title/Abstract] OR "systematic literature review*"[Title/Abstract] OR "meta analys*"[Title/Abstract] OR "case report*"[Title/Abstract] OR "case stud*"[Title/Abstract] OR "editorial"[Title/Abstract] OR "commentary"[Title/Abstract] OR "cochrane"[Title/Abstract] OR "Models, Animal"[MeSH] OR Review Literature as Topic OR Review [Publication Type] OR Systematic Review [Publication Type] OR Case Reports [Publication Type] OR Editorial [Publication Type] OR Comment [Publication Type] OR Systematic Reviews as Topic)
6	Timeframe	2015 - 2025	Pre-2015	NA
7	Combinations	(1 AND 2) NOT 5; Filters applied: in the last 10 years; English		

For women with PCOS, this protocol confers several important advantages. Most notably, it permits the use of a GnRH agonist trigger in place of hCG, a modification that has virtually eliminated the risk of OHSS in this population. In addition, it is associated with a shorter duration of analogue treatment, a reduced cumulative gonadotropin dose, and a markedly lower incidence of OHSS compared with traditional GnRH agonist long protocols [14-18]. More importantly, the American Society for Reproductive Medicine (ASRM) guidelines recommend the use of ovarian stimulation protocols with GnRH antagonists rather than GnRH agonists in patients at risk for OHSS [19]. In a systematic review and meta-analysis by Kadoura et al. (2022), GnRH antagonist protocols demonstrated several statistically significant advantages over long GnRH agonist protocols in controlled ovarian stimulation. Specifically, they were associated with a 42% reduction in the risk of OHSS (relative risk [RR]=0.58; 95% CI: 0.44 to 0.77; P=0.0002), a shorter stimulation duration by nearly one day (weighted mean difference [WMD]=−0.91; 95% CI: −1.45 to −0.37; P=0.0009), and reduced gonadotropin consumption by approximately 221 IU (WMD=−221.36; 95% CI: −332.28 to −110.45; P < 0.0001). It is important to note that higher estradiol levels have been associated with increased risk of OHSS in women receiving IVF [20]. In keeping with this, Kaduora et al. (2022) noted that estradiol levels on the day of human chorionic gonadotropin (hCG) administration were lower by about 259 pg/ml (WMD=−259.21; 95% CI: −485.81 to −32.60; P=0.02), and endometrial thickness was reduced by 0.73 mm (WMD=−0.73; 95% CI: −1.17 to −0.29; P=0.001). Additionally, the number of retrieved oocytes was modestly lower (WMD=−1.82; 95% CI: −3.48 to −0.15; P=0.03). Despite these differences, no significant variations were observed in live birth rate, ongoing pregnancy rate, clinical pregnancy rate, multiple pregnancy rate, miscarriage rate, or overall cycle cancellation rate between the two protocols. However, cycle cancellations due to poor ovarian response were more frequent in the antagonist group (RR=4.63; 95% CI: 1.49 to 14.41; P=0.008), while cancellations due to OHSS risk remained similar across both groups [11]. Safety advantages, coupled with comparable efficacy in pregnancy rates, make the GnRH antagonist protocol the strongly recommended first-line approach for women with PCOS [14,16,21]. Common variations include the flexible protocol, where GnRH antagonist administration typically commences when at least one follicle reaches 12 mm in diameter (usually between day 5 and day 8 of ovarian stimulation), continuing until the trigger day. Alternatively, a fixed protocol involves initiating the antagonist at a predetermined time, often around day 5-6 of ovarian stimulation [14].

A notable adaptation within the antagonist framework is the use of low-dose antagonist protocols, often termed "mini IVF"

Table 2. Reviews, systematic literature reviews, and meta-analyses on ART in women with PCOS published in English in the last 5 years.

S. No	Parameter	Eligibility	Ineligibility	Search string
1	Population	Women with polycystic ovary syndrome (PCOS)	People with any other condition	("Polycystic Ovary Syndrome"[MeSH] OR "polycystic ovary syndrom*"[Title/Abstract] OR "polycystic ovarian syndrom*"[Title/Abstract] OR "sclerocystic ovar*"[Title/Abstract] OR "Stein-Leventhal Syndrom*"[Title/Abstract] OR "Stein Leventhal Syndrom*"[Title/Abstract] OR "polycystic ovary disease"[Title/Abstract] OR "polycystic ovarian disease"[Title/Abstract] OR "PCOS"[Title/Abstract] OR "PCOD"[Title/Abstract])
2	Intervention	ART, IVF, ICSI, and related interventions	Any other intervention, such as IUI and artificial insemination	("Fertilization *in Vitro*"[Mesh] OR "Reproductive Techniques, Assisted"[Mesh] OR "Sperm Injections, Intracytoplasmic"[Mesh] OR "Assisted Reproductive Technics"[Title/Abstract] OR "Assisted Reproductive Technique"[Title/Abstract] OR "Assisted Reproductive Technology"[Title/Abstract] OR "Assisted Reproductive Technologies"[Title/Abstract] OR "*in vitro* fertilization"[Title/Abstract] OR "*in vitro* fertilisation"[Title/Abstract] OR "IVF"[Title/Abstract] OR "ICSI"[Title/Abstract] OR "Intracytoplasmic sperm injection*"[Title/Abstract] OR "Mitochondrial replacement therapy"[Title/Abstract] OR "Embryo transfer"[Title/Abstract] OR "Blastocyst transfer"[Title/Abstract] OR "FET"[Title/Abstract] OR "cryopreservation"[Title/Abstract] OR "fertility preservation"[Title/Abstract])
3	Comparator	Any comparator or no comparator	NA	Non-restrictive
4	Outcomes	IVF-related outcomes	NA	Non-restrictive
5	Study design	Review, SLRs, meta-analyses		("Narrative review*"[Title/Abstract] OR "Scoping review*"[Title/Abstract] OR "Systematic review*"[Title/Abstract] OR "systematic literature review*"[Title/Abstract] OR "meta analys*"[Title/Abstract] OR "cochrane"[Title/Abstract])
6	Timeframe	2020 - 2025	Pre-2020	NA
7	Combinations	1 AND 2 AND 5; Filters applied: English		

[22,23] Click or tap here to enter text.Click or tap here to enter text.. These protocols employ lower doses of gonadotropins (FSH and sometimes LH) or oral agents like clomiphene citrate or letrozole to stimulate ovarian follicular growth [23]. Some data have suggested that mini IVF protocols are associated with acceptable oocyte retrieval rates [24].

GnRH agonist protocol (Long protocol)

The GnRH agonist protocol is employed in *in vitro* fertilization to prevent an undesired spontaneous LH surge and to synchronize follicular development for oocyte retrieval. It has been implemented in several formats, most notably the long (downregulation) protocol and flare protocols. GnRH agonists act through a biphasic pharmacodynamic effect. Continuous administration first produces a transient flare effect, causing a surge in pituitary release of FSH and LH. Continued exposure then induces pituitary desensitization and prolonged downregulation. Historically, the GnRH agonist protocol was the standard for ovarian stimulation. However, this protocol has been noted to be associated with high risk of severe OHSS [25]. In a phase IV, dual center RCT by Toftager, et al. (2016), patients were randomized to a short GnRH antagonist or a long GnRH agonist protocol. The study found a significantly higher incidence of severe OHSS in the long agonist arm (8.9% *vs.* 5.1%; P=0.02) and a higher rate of moderate OHSS (15.6% *vs.* 10.2%; P=0.01). More women in the agonist group required physician review and hospital admission for OHSS, and ascites puncture occurred only in the agonist arm [25].

Triggering final oocyte maturation

GnRH agonist trigger

GnRH agonists are considered a first-line strategy to reduce the risk of moderate-to-severe OHSS in high-risk PCOS patients [26]. Across studies, GnRH agonist treatment has been shown to improve outcomes in women with PCOS [17,27]. Specifically, GnRH trigger has been demonstrated to contributes to a lower OHSS risk [28]. In a retrospective study by Deepika et al. (2021), comparing GnRH agonist and hCG triggers, the odds of achieving a cumulative live birth per stimulation cycle were significantly higher with GnRH agonist when compared with hCG trigger (odds ratio [OR] 2.15; 95% CI 1.2 to 3.83; P=0.008). The GnRH agonist group also produced more mature oocytes (P<0.001) and blastocysts (P<0.001) than the hCG group [29]. In an earlier study, Nadkarni et al. (2017) performed a double blinded comparative assessment of 100 PCOS patients receiving GnRH agonist and hCG triggers. Group A (GnRH agonist, n=50) achieved 31 pregnancies, while Group B (hCG, n=50) had 29, showing no significant difference (P>0.05). However, OHSS incidence was markedly lower with GnRH agonist: mild OHSS significantly reduced (P<0.05), moderate OHSS similar (P>0.05), and no severe OHSS in either group [30]. These results support the use of GnRH agonist trigger to improve both oocyte yield and cumulative live birth outcomes.

Human Chorionic Gonadotropin (HCG) trigger

Human chorionic gonadotropin has been traditionally employed to trigger final oocyte maturation. However, hCG has been noted to carry a higher risk of OHSS in PCOS patients. In the retrospective study by Deepika et al. (2021), comparing GnRH agonist and hCG triggers, the risk of OHSS was considerably higher for hCG trigger relative to GnRH agonist (47.4% *vs.* 0.52%; P<0.001) [30]. Therefore, the hCG trigger is often avoided in high-risk PCOS patients in favor of GnRH agonist triggers or a "freeze-all" strategy [31].

Dual trigger (GnRH agonist + Low-dose HCG)

The dual trigger approach combines the GnRH agonist trigger with low-dose hCG. Considerable evidence suggests that dual trigger is associated with higher risk of OHSS but improvements in total and mature oocyte counts [32,33]. In an early retrospective study, by O' Niel et al. (2016), dual trigger was linked to a higher total oocyte yield (adjusted OR 1.27; 95% CI 1.18 to 1.38) and an increased mature oocyte rate (adjusted OR 1.10), but was associated with a notably higher risk of early OHSS (8.6% *vs.* 0% with GnRHa trigger) [32]. In another retrospective study by Shapiro et al. (2021), in the dual-trigger group, patients were younger (33.6 *vs.* 34.1 years), had higher AMH (6.3 *vs.* 4.9 ng/mL), more oocytes retrieved (18.1 *vs.* 14.9) and a greater fertilization rate (80% *vs.* 77%), yet they experienced lower clinical pregnancy (43.4% *vs.* 52.8%) and live birth rates (33.4% *vs.* 45.8%) than the hCG-only group [34].

Alternative stimulation approaches

Beyond the established GnRH-based protocols, several innovative approaches are being investigated to further refine ovarian stimulation for women with PCOS, particularly focusing on safety and patient experience.

In Vitro Maturation (IVM)

IVM represents an evolving treatment option designed to avoid or substantially reduce the risk of OHSS by minimizing or entirely eliminating the use of gonadotropins for ovarian stimulation [26]. This approach is particularly advantageous for women with PCOS, who are inherently at a high risk for OHSS [26,35] Click or tap here to enter text. The IVM protocol involves retrieving immature oocytes with minimal or no prior hormonal stimulation, followed by their maturation *in vitro* before fertilization *via* intracytoplasmic sperm injection (ICSI) [26,36].

Current evidence suggests that while IVM offers a patient-friendly approach with virtually no OHSS risk, it has historically been associated with a lower cumulative live birth rate compared to conventional IVF [37]. In an early observational study by Das, et al. (2014), IVM was noted to be associated with considerably lower risk of OHSS [38]. In a recent RCT, Vuong et al. (2025) demonstrated that CAPA IVM with or without 2 days of FSH priming produced similar oocyte maturation and embryology outcomes in women with PCOS. Median matured oocytes were 13 (IQR 9–18) without FSH *vs.* 14 (IQR 7–18) with FSH (absolute difference −1; 95% CI −5 to 4). Ongoing pregnancy and live birth rates were 38.3% *vs.* 31.7% (RR 1.21; 95% CI 0.74 to 1.98). Maternal complications were infrequent and comparable between groups. These findings indicate that CAPA IVM without FSH priming yields equivalent maturation, embryology, and pregnancy outcomes to FSH primed CAPA IVM, supporting a feasible, hormone sparing option for women with PCOS [39]. More recently, introduction of a prematuration step has been shown to improve maturation and clinical pregnancy rates [40]. A non-inferiority randomized clinical trial is currently underway to directly compare live birth rates between IVM and standard IVF for women with PCOS [41,42]. This situation highlights a critical clinical consideration of the balance between safety and efficacy. IVM significantly enhances safety by mitigating OHSS risk, a major concern in PCOS Click or tap here to enter text [26,38].

In a systematic review and meta-analysis by Xu and Qiao (2021), IVM had similar clinical effects compared with IVF in patients with PCOS in terms of clinical pregnancy rates although live birth rates were lower [43]. It has been recommended that decisions regarding IVM must carefully weigh the individual patient's risk of OHSS against their ultimate goal of achieving the highest possible live birth success. This necessitates thorough counseling to ensure that patients understand the trade-offs involved, and ongoing research is vital to bridge this efficacy gap.

Progestin-Primed Ovarian Stimulation (PPOS)

PPOS is a newer ovarian stimulation method that employs oral progestins, such as dydrogesterone or medroxyprogesterone acetate, administered from the early follicular phase until the trigger day [44-46]. This strategy effectively suppresses the premature LH surge during ovarian stimulation, offering a viable alternative to GnRH analogues for pituitary suppression [44-47].

PPOS protocols present several advantages [48,49], including the convenience of oral administration [44], a reduced burden of injections for patients, potentially lower drug costs, and effective control over LH levels, which contributes to a reduced OHSS risk [44-46]. In a systematic review and meta-analysis by Yang et al. (2023), the efficacy of PPOS in women with PCOS was assessed. This systematic review evaluated the efficacy of PPOS compared to conventional GnRH analogue protocols in women with PCOS undergoing IVF or ICSI. Across three RCTs and six cohort studies involving 2,289 patients, PPOS showed no significant difference in live birth rate, OHSS risk, or metaphase II oocyte yield compared to GnRH analogues (P>0.05). However, cohort data suggested that PPOS may improve implantation, clinical pregnancy, and ongoing pregnancy rates, particularly when compared to the GnRH agonist short protocol, though the certainty of evidence remains low [50]. Due to the potential impact of progestins on endometrial receptivity, PPOS protocols are strongly associated with a "freeze-all" embryo transfer strategy, where all embryos are cryopreserved for later Frozen Embryo Transfer (FET) [51]. This strategy has demonstrated higher ongoing pregnancy and live birth rates in women with PCOS compared to fresh transfers in data from RCTs [52]. The features of PPOS, such as oral administration and reduced injection frequency, directly address common patient burdens in IVF, including discomfort from daily injections [44]. This indicates that PPOS represents a significant advance toward more patient-friendly and potentially more accessible IVF protocols, which can enhance patient

adherence and overall treatment experience, even if the primary clinical outcomes are comparable to other effective protocols [45]. However, some findings point to potential deterioration in oocyte quality in response to PPOS use. However, studies suggest PPOS is associated with a lower live birth rate compared to GnRH antagonist protocols. In this regard, in a retrospective cohort study by Handa et al. (2025), PPOS (n=299) *vs.* GnRH-antagonist (n=608) reduced premature LH surge (3.1% *vs.* 20.1%, OR 0.13) but was associated with worse embryology and outcomes: lower good-quality cleavage embryo rate (37.2% *vs.* 49.1%) and lower live birth after first FET (31.5% *vs.* 42.3%, OR 0.63). Additionally, single-cell RNA-seq of mural granulosa cells showed up regulation of 12 mtDNA genes with PPOS, suggesting impaired oocyte quality [52].

Adjunctive therapies

Various medications are utilized as adjuncts in IVF protocols for PCOS patients, aiming to improve ovarian response, oocyte quality, and reduce complications.

Metformin

Metformin, an insulin-sensitizing agent, is widely incorporated into PCOS management to improve insulin sensitivity and reduce androgen levels [53,54]. It is important to note that the beneficial impact of metformin in PCOS patients has shown inconsistent outcomes. Some findings report benefits of metformin treatment in PCOS patients receiving IVF in demonstrating reductions in the risk of OHSS [55-57]. A meta-analysis of 12 RCTs including 1,123 women with PCOS undergoing IVF/ICSI-ET by Wu, et al. (2020) found that metformin reduced the risk of OHSS (OR 0.43, 95% CI 0.24 to 0.78). The protective effect was not significant in women with BMI <26 (OR 0.67, 95% CI 0.30 to 1.51). Across the total population there were no significant differences in clinical pregnancy (OR 1.24, 95% CI: 0.82 to 1.86) or live birth rates (OR 1.23, 95% CI 0.74 to 2.04). A post hoc analysis showed higher clinical pregnancy rates with metformin in women with BMI ≥ 26 (OR 1.71, 95% CI 1.12 to 2.60) [56]. In a systematic review by Leopoldo et al. (2020), 13 RCTs involving 1132 women with PCOS undergoing IVF/ICSI were analyzed. With long GnRH agonist stimulation, metformin showed uncertain effects on live birth (RR 1.30, 95% CI 0.94 to 1.79) but may increase clinical pregnancy rates (RR 1.32, 95% CI 1.08 to 1.63). In contrast, with GnRH antagonist protocols, metformin may reduce live birth (RR 0.48, 95% CI 0.29 to 0.79) and its impact on clinical pregnancy remains uncertain. Metformin also reduced OHSS risk (RR 0.46, 95% CI 0.29 to 0.72) [58]. Additionally, in a placebo controlled RCT in 120 high risk women with PCOS undergoing gonadotropin stimulation for IVF, Palomba, et al. (2011) compared metformin 500 mg TID *vs.* placebo. Metformin significantly reduced total OHSS and cancellation rates (RR 0.28; 95% CI 0.11 to 0.67), lowered peak estradiol, and lengthened stimulation with higher gonadotropin use [59]. These findings supported metformin as an OHSS risk reduction strategy in PCOS clinical practice. Adjunct metformin therapy can be initiated before and/or during FSH ovarian stimulation. Metformin can also enhance clinical pregnancy rates and decrease the risk of early pregnancy loss in PCOS patients [55]. While effective as an adjunct, metformin alone is generally less potent for ovulation induction compared to letrozole or clomiphene citrate.

Myo-inositol and N-Acetylcysteine (NAC)

Myo-inositol, another insulin-sensitizing compound, has demonstrated efficacy in improving insulin sensitivity, metabolic markers, and ovarian function in women with PCOS [60]. Its use in IVF cycles can reduce OHSS risk and enhance oocyte quality [61, 62]. It has also been demonstrated that N-acetylcysteine (NAC) may improve oocyte quality and has shown potential to enhance ovulation and pregnancy rates when combined with letrozole [63]. In a placebo-controlled RCT by Mostajeran et al. (2018), in women receiving letrozole plus N-acetylcysteine, the follicle count exceeding 18 mm rose significantly (P=0.007), and both ovulation and pregnancy rates improved markedly (P=0.045). Additionally, no adverse events or cases of OHSS were reported [64]. Similar findings were noted in another RCT in which, infertile women with PCOS were allocated to receive either letrozole plus NAC or letrozole plus placebo. The letrozole + NAC arm produced significantly larger dominant follicles (16.6 ± 3.3 mm *vs.* 15.1 ± 3.9 mm; P=0.004) and doubled the ovulation induction rate (32.3% *vs.* 15.6%; P=0.006) compared with placebo. Furthermore, pregnancy success was significantly higher in the NAC group (17 *vs.* 7 pregnancies; P=0.029) [64]. Additionally, in a study by Sacchinelli et al. (2014), 91 infertile women with PCOS, with or without insulin resistance, were treated with Ovaric HP (inositol plus N acetyl cysteine and folic acid). The intervention improved ovulation and menstrual regularity, and notably, pregnancy was achieved in a subset of patients, indicating enhanced ovarian function irrespective of insulin resistance status [65].

Thiazolidinediones (TZDs)

Thiazolidinediones (TZDs), including pioglitazone and rosiglitazone, are insulin sensitizers that activate PPARγ receptors, primarily in adipocytes and muscle cells. This action leads to improved insulin sensitivity and can potentially reduce androgen secretion. Clinical evidence indicates that TZDs can lead to comparable ovulation rates and pregnancy success in PCOS patients, when compared with clomiphene citrate [66]. In an interventional non-RCT, follicle size was comparable between patients receiving combination of pioglitazone and clomiphene citrate *vs.* clomiphene citrate alone (P=0.742). Pregnancy rates were also similar (P=1.000) [66].

Statins

No findings clearly demonstrate the benefits of statins on reproductive outcomes [67]. In this regard, a systematic review and meta-analysis conducted by Xiong et al. (2023) has further highlighted the uncertainty on the outcomes of statin treatment among women with PCOS [68].

Laparoscopic ovarian drilling

Laparoscopic Ovarian Drilling (LOD), also referred to as laparoscopic ovarian surgery, is a surgical treatment option designated as a second-line intervention for women with Clomiphene Citrate (CC)-resistant PCOS. The procedure involves the use of thermal energy (diathermy) to make targeted punctures

aimed at reducing intraovarian androgen production, which rapidly normalizes LH and testosterone levels. A systematic review and meta-analysis specifically evaluated LOD against metformin (with or without CC) for clomiphene-resistant women with PCOS, suggesting its role in improving reproductive outcomes [69]. LOD can be considered as a preparatory step before IVF/ICSI for high responders, as it has been shown to reduce the risk of OHSS in subsequent ART cycles. Specifically, for PCOS patients with high Anti-Müllerian Hormone (AMH>7 ng/ml) undergoing IVF/ICSI, LOD reduces gonadotropin consumption and stimulation days, increases the percentage of collected mature oocytes, and significantly decreases the incidence of severe OHSS, though it may not improve overall pregnancy or implantation rates [70]. Notably, in CC-resistant women with a previous history of severe OHSS, LOD provided superior prophylaxis (0% incidence of severe OHSS) and a significantly higher pregnancy rate (67%) compared to a GnRH antagonist combined with cabergoline [71].

Embryo transfer strategies

Fresh Embryo Transfer (Fresh ET)

Fresh ET in women with PCOS involves transferring embryos into the uterus during the same cycle as ovarian stimulation and oocyte retrieval. While generally successful in non-PCOS patients, its application in PCOS requires careful consideration due to the high OHSS risk and the impact of supraphysiological hormone levels on the endometrium. In PCOS patients, fresh ET carries a higher risk of OHSS and may be associated with adverse perinatal outcomes compared with frozen transfer in some studies. Wong, et al. (2021) conducted an RCT comparing a freeze-all strategy (see below) with conventional fresh plus frozen transfer and reported a significantly lower cumulative ongoing pregnancy rate with freeze-all: 19% (19/102) *vs.* 31% (32/102); relative risk 0.59 (95% CI 0.36 to 0.98) [72]. In an earlier study, Lattes et al. (2020) reported a retrospective cohort from Spain of 1,882 first embryo transfer cycles comparing fresh *vs.* frozen transfers and found that live birth rates were higher with frozen transfers in women 38 years (19.8% *vs.* 12.7%, P=0.07; OR 0.96) [73].

"Freeze-all" Strategy

Freeze-all strategy involves cryopreserving all embryos after oocyte retrieval and deferring embryo transfer to a subsequent cycle. It has been widely adopted for PCOS patients [74,75]. Beyond OHSS prevention, the "freeze-all" strategy also allows for embryo transfer in a more physiologically receptive endometrial environment [76].

Studies have shown that, compared to fresh embryo transfer, the "freeze-all" strategy can yield comparable or even higher rates of live birth in women with normal or good prognosis [77]. In a large RCT by Chen et al. (2016), based on 1,508 women with PCOS, cycle segmentation reduced the rate of OHSS to 1.3% *vs.* 7.1% in conventional fresh embryo transfer, while also improving the live birth rate after the first transfer (49.3% *vs.* 42%) [78]. Specifically for women with PCOS, FET has resulted in a higher frequency of live births and a lower frequency of pregnancy loss and OHSS compared with fresh embryo transfer [78]. Furthermore, the "freeze-all" approach facilitates the accumulation of oocytes or embryos from potentially multiple retrieval cycles, allowing for several transfers from a single retrieval, which often leads to higher cumulative live birth rates [79].

Individualized protocol adaptations based on patient characteristics

Tailoring IVF protocols to individual patient characteristics is paramount for optimizing outcomes and minimizing risks in women with PCOS, who exhibit significant heterogeneity.

By body weight

Body weight, particularly body mass index (BMI), exerts a substantial influence on IVF outcomes in women with PCOS.

Impact of overweight and obesity on IVF outcomes in PCOS

Overweight and obese women with PCOS undergoing IVF-ET consistently demonstrate poorer reproductive outcomes compared to their normal-weight counterparts [80-82]. Studies indicate a reduction in the number of oocytes retrieved and fewer good-quality embryos. In a systematic review and meta-analysis by Alenezi, et al. (2024), 19 studies involving 7680 women with PCOS undergoing IVF were analyzed to assess the impact of high BMI. Women with normal BMI had significantly higher odds of clinical pregnancy (OR=1.16, 95% CI 1.04 to 1.29) and live birth (OR=1.88, 95% CI 1.56 to 2.27). High BMI was associated with increased miscarriage risk (OR=0.76, 95% CI 0.60 to 0.95). Pooled analyses also demonstrated elevated risks of gestational diabetes (OR=3.96, 95% CI 1.62 to 9.68), gestational hypertension (OR=2.16, 95% CI 1.32 to 3.54), and caesarean section (OR=0.45, 95% CI 0.29 to 0.69) [83]. Specifically, live birth rates are significantly diminished with increasing BMI; for instance, a study reported live birth rates of 35.7% for normal-weight, 30.6% for overweight, and 27.2% for obese women with PCOS [81,83-85]. A national study in the US by Hynes et al. (2022) further revealed a decline in favorable perinatal outcomes (defined as a singleton live birth at or after 37 weeks with appropriate birth weight) from 22.7% in normal-weight to 12.2% in class III or super obese women with PCOS [86]. Furthermore, overweight and obese women with PCOS experience higher rates of both early and late miscarriage [84,87-89].

Given these findings, addressing obesity through interventions such as weight loss prior to IVF treatment is crucial for improving oocyte and embryo quality and increasing live birth rates. This underscores the necessity of integrated care models that include lifestyle modifications and weight management as integral parts of the fertility treatment plan. In this regard, patient counseling should emphasize that the likelihood of achieving a good perinatal outcome diminishes as body weight increases [90,91].

By age

Maternal age is a well-established determinant of IVF success across all patient populations, with live birth rates generally declining with advancing age [92-94].

Women with PCOS often maintain a relatively preserved ovarian reserve, reflected by higher Anti Müllerian Hormone (AMH) levels

compared to age matched non PCOS women. This physiological feature can translate into a higher oocyte yield during stimulation. Notably, studies have reported that women with PCOS aged 35 years or older may achieve higher cumulative live birth rates over a two year period compared with age and BMI matched controls with tubal factor infertility. These findings suggest that although the age related decline in fertility affects women with PCOS similarly to the general population, their ovarian reserve advantage may attenuate this decline and, in certain contexts, confer relatively better reproductive outcomes in older age groups undergoing IVF than non PCOS counterparts. Importantly, this observation should be interpreted as a relative difference in treatment response rather than an inherent protective effect of PCOS, underscoring the need for cautious clinical application and further confirmatory studies [95,96]. Additionally, advancing age in women with PCOS is associated with increased oocyte aneuploidy, mitochondrial dysfunction, and loss of cellular polarity, which may collectively impair embryonic developmental competence and increase the risk of pregnancy loss.

By ethnicity

The influence of ethnicity on IVF protocols for PCOS is a complex area with recognized gaps in specific guidelines [17-97]. Current international guidelines often provide generalized recommendations, emphasizing that their application necessitates consideration of individual patient characteristics and preferences [98]. Clinical characteristics of PCOS and infertility frequently vary across ethnic groups [99-102]. International guidelines also recommend that BMI categories and waist circumference measurements should consider ethnic and adolescent ranges, with specific attention to Asian and other high-risk ethnic groups [97,103]. In line with this, in a large retrospective cohort study, Calderon et al. (2025) analyzed 128,703 IVF cycles in the USA to assess racial disparities. Live birth rates were highest in white women (PCOS 49.5%, non PCOS 45.1%) and lowest in African American women (PCOS 36%, non PCOS 34.3%). African American and Asian women with PCOS had significantly lower odds of live birth, while pregnancy loss and neonatal death risks were elevated in minority groups. These findings highlight substantial racial and ethnic disparities in reproductive and neonatal outcomes among women with infertility, both with and without PCOS, undergoing IVF in the United States [99].

Discussion

Summary of clinical IVF outcomes in women with PCOS

The findings of this structured literature review suggest that contemporary ovarian stimulation strategies for women with PCOS are best implemented through phenotype driven, risk stratified care rather than a single standardized pathway. Objective pre cycle assessment (AMH, antral follicle count, BMI, metabolic profile) should be used to estimate OHSS risk and to align stimulation intensity with patient priorities (speed of conception, tolerance for injections, willingness to accept freeze all). Translating trial results into practice therefore requires three linked actions: routine risk stratification, explicit shared decision making those documents the tradeoffs between safety and immediacy of transfer, and local audit of outcomes (OHSS rates, cycle cancellations, cumulative live birth). When these steps are embedded in clinical workflows, centers can reduce severe complications, shorten inpatient care needs, and preserve cumulative live birth potential across cycles.

Pooled evidence in this review supports that GnRH antagonist protocols reduce OHSS incidence, shorten stimulation duration and lower gonadotropin consumption while producing broadly comparable clinical pregnancy and live birth rates to long agonist regimens. Trigger day estradiol and endometrial thickness were modestly lower with antagonists and retrieved oocyte number was slightly reduced; some series reported higher cancellations for poor response in antagonist arms. Across studies, GnRH antagonist protocols were noted to offer clinical advantages over long GnRH agonist protocols, including reduced OHSS risk, shorter stimulation duration, ability to use agonist trigger, and lower hormonal exposure. Despite these benefits, pregnancy and live birth outcomes remain comparable between the two approaches. However, antagonist protocols are more likely to result in cycle cancellations due to poor ovarian response [11]. Alternatively, short “flare” protocols harness the initial agonist-induced surge of gonadotropins to augment follicular recruitment in poor responders. Furthermore, GnRH antagonism has also been shown to be relatively safe with manageable safety profiles [14,16,21]. Together, these agonist regimens minimize cycle cancellations, optimize oocyte yield and quality, and reduce the incidence of premature LH surges [11,14,16,21].

Triggering strategies for final oocyte maturation are critical in mitigating OHSS risk and optimizing IVF success. GnRH agonist triggers are preferred in high-risk PCOS patients due to their ability to suppress OHSS while maintaining favorable reproductive outcomes [67]. Retrospective data show that GnRH agonist triggers yield more mature oocytes and blastocysts and are associated with higher cumulative live birth rates compared to hCG triggers [17,30,104]. In contrast, hCG triggers, though traditionally used, carry a substantially higher OHSS risk and are often avoided in PCOS patients, especially when fresh embryo transfer is planned [30,32]. The dual trigger approach, combining GnRH agonist with low-dose hCG, aims to enhance oocyte maturation and fertilization rates. While it improves oocyte yield and maturity, it also increases the risk of early OHSS. Moreover, despite higher fertilization rates, dual trigger protocols have been associated with lower clinical pregnancy and live birth rates compared to hCG-only triggers in some studies [35].

IVM is an emerging alternative to conventional IVF that has been shown to substantially mitigate OHSS by minimizing or avoiding gonadotropin stimulation; prematuration strategies reported in the review improve the proportion of oocytes reaching metaphase II and increase mature oocyte yield. Despite these, clinical outcomes may still report lower cumulative live birth rates with IVM compared with conventional stimulated IVF, implying that embryo development and blastulation after IVM often lag behind conventional protocols in routine practice. In practical terms, IVM may be most appropriate for patients with extreme OHSS susceptibility (very high AMH/AFC), prior severe OHSS, contraindications to gonadotropin exposure, or for those

willing to accept embryo accumulation across multiple minimal stimulation cycles. Consequently, when counselling patients, IVM may be presented as a tradeoff between the near elimination of OHSS risk *vs.* generally lower cumulative live birth probability and often lower blastocyst formation rates.

The assembled data indicate that PPOS, when paired with planned freeze all, achieves live birth outcomes comparable to antagonist protocols in many series. In pooled analyses (three RCTs and six cohort studies) PPOS showed no significant difference in live birth, OHSS risk or metaphase II yield compared with GnRH analogues, although some cohort data suggest possible improvements in implantation and ongoing pregnancy in specific comparisons. This approach matches conventional antagonist protocols in oocyte and embryo quality while virtually eliminating OHSS risk, highlighting its clinical advantage in safety. It is important to note that because PPOS necessitates cryopreservation, any marginal endometrial effects of progestin exposure are bypassed, and implantation and live birth in FET cycles are generally preserved. The main limitations of PPOS may be the need for reliable vitrification and timely FET access. In keeping with this, when recommending PPOS, clinicians may discuss operational implications (timing of transfer, potential delays, cryostorage costs and local FET success rates) and ensure patients understand that PPOS preserves pregnancy and live birth probabilities when used within a freeze all pathway. Cohort data indicate potential improvements in implantation, clinical pregnancy, and ongoing pregnancy rates with PPOS, especially compared to the GnRH agonist short protocol, suggesting possible clinical benefits that should be taken into consideration. Although the certainty of evidence is low, PPOS remains a clinically viable and patient-friendly option, particularly when frozen-thawed embryo transfer is planned, emphasizing its utility in balancing convenience, safety, and reproductive outcomes [50].

Treatment strategies for PCOS also include a range of adjunctive therapies and triggering protocols aimed at optimizing ovarian response, improving oocyte quality, and minimizing OHSS. Among adjunctive therapies, metformin remains widely used due to its insulin-sensitizing and anti-androgenic effects [54,55]. While its impact on IVF outcomes has been inconsistent, metformin may reduce OHSS risk and improve clinical pregnancy rates when administered before or during stimulation [56-58]. However, it is generally less effective for ovulation induction compared to agents like letrozole or clomiphene citrate. Other adjuncts include myo-inositol and NAC, both of which improve insulin sensitivity and metabolic profiles [61]. Myo-inositol has shown potential in enhancing oocyte quality and reducing OHSS risk during IVF cycles. NAC, particularly when combined with letrozole, has demonstrated significant improvements in follicular development, ovulation rates, and pregnancy outcomes without increasing OHSS risk [62,63]. Randomized controlled trials have reported larger dominant follicles and higher ovulation and pregnancy rates in NAC-treated groups compared to placebo [64,65]. TZDs, such as pioglitazone and rosiglitazone, also improve insulin sensitivity *via* PPARγ activation and may yield comparable ovulation and pregnancy rates to clomiphene citrate, though evidence remains limited [67]. Statins, despite their metabolic benefits, currently lack robust evidence supporting improvements in reproductive outcomes for PCOS patients [67].

The available evidence also indicates that the use of cycle segmentation and a freeze-all approach significantly reduces the incidence of OHSS and may enhance first-transfer live birth rates. Notably, a large randomized controlled trial referenced herein reported an OHSS incidence of 1.3% in the freeze-all group compared to 7.1% in the fresh transfer group, with corresponding first-transfer live birth rates of 49.3% *vs.* 42%, respectively [79]. The freeze-all strategy also mitigates the risk of OHSS-related cycle cancellations and facilitates embryo transfer in a more physiologically receptive endometrial environment, which, as demonstrated in several trials, is associated with improved implantation and first-transfer live birth rates. These findings suggest that the freeze-all strategy may strongly be considered for patients at increased risk of OHSS, those exhibiting supraphysiologic serum estradiol concentrations, or when a GnRH agonist trigger is employed. Successful implementation necessitates robust vitrification infrastructure, reliable scheduling for FET, and comprehensive patient counselling regarding possible procedural delays and associated costs. For patients at low risk of OHSS who prioritize rapid conception, FET remains a reasonable option. Conversely, in high-risk individuals, the freeze-all approach should be presented as the strategy most likely to minimize immediate maternal morbidity while maintaining or potentially enhancing cumulative live birth outcomes.

The review indicates consistent modifier effects that should inform individualized care. Overweight and obesity are associated with reduced oocyte yield and live birth, and adverse perinatal outcomes decline with increasing BMI [81-86]. Age remains the dominant determinant of oocyte quality, but women with PCOS often retain higher AMH and oocyte yield [93-95]; several studies suggest that women with PCOS aged 35 years or older may achieve higher cumulative live birth rates over two years compared with age and BMI matched tubal factor controls, implying preserved reserve can partially attenuate age related decline [38,96,105,106]. Ethnicity modifies metabolic phenotype expression and risk thresholds [97-99,101,102]; clinicians should apply ethnicity specific BMI and metabolic screening cutoffs and provide appropriate counselling [92,100,102,103].

Integrating these strategies into a flexible, phenotype-driven algorithm enables fertility specialists to optimize both immediate and long-term reproductive outcomes. By aligning protocol selection with individual risk profiles, clinics can enhance patient comfort, streamline workflow, and maximize cumulative live birth rates.

Research Gaps and Future Directions

Significant research gaps remain in the understanding and management of PCOS in the context of IVF, pointing towards exciting future directions. Characterization of the proportion of women with PCOS who undergo IVF remains a substantial data gap. Population level estimates are scarce and inconsistent across regions, and existing studies often lack standardized definitions of PCOS, clear denominators, or longitudinal follow up. This limits our ability to quantify demand for assisted reproduction,

to identify disparities in access, and to tailor prevention or treatment strategies; establishing harmonized registries and routine reporting would clarify uptake, inform resource planning, and guide evidence based policy for this high risk group. The inherent clinical heterogeneity and unclear pathogenesis of PCOS continue to pose challenges for precise diagnosis and truly individualized treatment. Future research must deepen the understanding of its etiological mechanisms, encompassing genetics, epigenetics, and the role of the gut microbiota.

In terms of ovarian stimulation protocols, continued development and validation of mild and minimal ovarian stimulation approaches are crucial to optimize oocyte yield while further minimizing OHSS risk. Further investigation into LH-based flexible GnRH antagonist protocols and PPOS protocols is needed to enhance their efficacy and safety profiles. Exploration of new gonadotropin formulations and refined dose adjustment strategies will also contribute to improved outcomes. For adjunctive therapies, further research is necessary to refine the optimal dose, timing, and combination of agents like myo-inositol and NAC.

Collectively, these research areas indicate a clear paradigm shift from generalized protocols to a precision medicine approach. Future IVF treatment for PCOS will be increasingly tailored based on an individual patient's unique molecular, metabolic, and genetic profile. This evolution will move beyond current broad demographic factors (age, BMI, ethnicity) to truly individualized protocols, ultimately maximizing efficacy and safety while minimizing patient burden and cost through highly targeted interventions. This represents the cutting edge of reproductive endocrinology and promises a more effective and personalized future for women with PCOS seeking fertility treatment.

Conclusion and Future Directions

The management of infertility in women with PCOS undergoing IVF has significantly advanced, primarily driven by a deeper understanding of the syndrome's heterogeneity and the imperative to mitigate OHSS risk. GnRH antagonist protocols have emerged as the preferred first-line stimulation strategy due to their superior safety profile and comparable efficacy to older agonist protocols. Emerging approaches like IVM and PPOS offer innovative avenues, balancing safety with patient convenience and potentially lower costs, albeit with ongoing evaluation of their long-term efficacy.

Individualized protocol adaptations are crucial, with body weight profoundly influencing IVF outcomes, necessitating pre-treatment weight management. While age generally impacts IVF success, PCOS patients may exhibit a relative advantage in ovarian reserve compared to age-matched controls. The significant variations in PCOS phenotypes and treatment responses across different ethnic groups highlight a critical need for more tailored, evidence-based protocols to ensure equitable and optimal care globally. Adjunctive therapies, such as metformin and myo-inositol, play a vital role in improving metabolic parameters and reducing OHSS risk, though their precise application requires further refinement. The strategic use of GnRH agonist triggers and the widespread adoption of "freeze-all" embryo transfer strategies are pivotal in balancing OHSS prevention with maximizing live birth rates, by optimizing both ovarian safety and endometrial receptivity.

Despite these advancements, challenges persist, including the ongoing management of OHSS, the financial and emotional burden on patients, and the risk of pregnancy complications. Future research must focus on deepening the understanding of PCOS pathogenesis at a molecular level, developing novel stimulation protocols that are even more personalized, and refining the use of adjunctive therapies. In summary, this review underscores the value of a multi¬modal approach to ovarian stimulation in PCOS. Harnessing the complementary strengths of GnRH agonist downregulation, PPOS, and IVM builds on traditional stimulation metrics to foster safer cycles, improve patient satisfaction, and ultimately achieve superior fertility outcomes.

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