



Comparison between Progesterone-Primed Protocol and GnRH Antagonist Protocol on Oocyte Yield and Fertilization Rate in PCOS Females

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ABSTRACT

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Polycystic ovary syndrome (PCOS) is a common cause of anovulatory infertility and is associated with an increased risk of premature luteinizing hormone (LH) surges during controlled ovarian stimulation. Progestin-primed ovarian stimulation (PPOS) using Medroxyprogesterone Acetate (MPA) has emerged as a convenient alternative to conventional gonadotropin-releasing hormone (GnRH) antagonist protocols. This study aimed to compare the effects of MPA-based PPOS and GnRH antagonist protocols on oocyte yield, maturation, fertilization, and embryo quality in women with PCOS undergoing ICSI. This prospective, randomized, open-label controlled clinical trial included 108 women with PCOS undergoing ICSI at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, Baghdad, Iraq, between 2023 and 2024. Participants were allocated to an MPA-based PPOS group (n=49) or a flexible GnRH antagonist group (n=59). Oocyte yield, metaphase II (MII) oocytes, fertilization rate, embryo quality, ovarian sensitivity index (OSI), gonadotropin consumption, stimulation duration, and LH profiles were evaluated. No significant differences were observed in baseline characteristics or hormonal profiles between groups. The MPA group showed a numerically higher number of retrieved oocytes (20.65 ± 7.50 vs. 13.39 ± 4.41 ; $p=0.083$) and MII oocytes (15.10 ± 5.20 vs. 11.24 ± 4.12 ; $p=0.09$), although these differences were not statistically significant. Fertilization rates were comparable between groups ($72.4 \pm 10.6\%$ vs. $71.2 \pm 11.3\%$; $p=0.68$), as were embryo quality, OSI, gonadotropin consumption, and stimulation duration. Both protocols effectively suppressed premature LH surges without premature ovulation or cycle cancellation. MPA-based PPOS appears to be an effective and practical alternative to GnRH antagonist protocols for PCOS patients undergoing ICSI, providing comparable fertilization and embryological outcomes with effective LH suppression. Its oral administration and potential cost advantages may be particularly valuable in resource-limited ART settings.

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KEYWORD

PCOS; PPOS; MPA; GnRH antagonist; ICSI; Oocyte yield; Fertilization

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine disorders in women of reproductive age, affecting approximately 6–15% of this population worldwide and accounting for up to 80% of cases of anovulatory infertility [1,2]. Characterized by hyperandrogenism, oligo/anovulation, and polycystic ovarian morphology, PCOS is a multifactorial syndrome associated not only with reproductive dysfunction but also with significant metabolic and psychological consequences [3,4]. The complex pathophysiology of PCOS involves a dysregulated hypothalamic–pituitary–ovarian (HPO) axis, insulin resistance, and hyperinsulinemia, all contributing to disrupted folliculogenesis and a propensity for excessive ovarian response during controlled ovarian stimulation (COS) [5,6].

Assisted reproductive technologies (ART), including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), remain essential treatment strategies for women with PCOS-related infertility who do not respond to first-line ovulation induction agents [7]. However, the hyper-responder nature of PCOS patients increases their risk for premature luteinizing hormone (LH) surges and ovarian hyperstimulation syndrome (OHSS) during COS [8,9]. Premature LH surges can lead to premature ovulation, cycle cancellation, suboptimal oocyte retrieval, and impaired embryo quality, ultimately compromising ART outcomes [10].

To prevent premature LH surges, gonadotropin-releasing hormone (GnRH) antagonists have been traditionally used in flexible or fixed COS protocols. These agents rapidly and reversibly suppress LH secretion via competitive inhibition at the GnRH receptor level in the anterior pituitary [11]. Despite their effectiveness, GnRH antagonists present several limitations, including the need for daily subcutaneous administration, higher costs, and potential discomfort, which may affect patient compliance and accessibility—especially in resource-constrained settings [12].

An emerging alternative to GnRH antagonists is the use of oral progestins, particularly Medroxyprogesterone Acetate (MPA), as part of progestin-primed ovarian stimulation (PPOS) protocols. MPA suppresses LH surges through negative feedback on the hypothalamus, reducing GnRH pulsatility [13]. This oral regimen offers a cost-effective, well-tolerated, and convenient approach to COS, especially advantageous in hyper-responders such as PCOS patients [14]. However, the impact of MPA on endometrial receptivity necessitates embryo cryopreservation and deferred frozen-thawed embryo transfer, a trade-off that must be balanced against its benefits [15]. While both protocols aim to optimize follicular recruitment and prevent premature ovulation, few high-quality randomized studies have rigorously compared their effects on critical embryological outcomes in PCOS patients, such as oocyte yield, fertilization rate, and ovarian sensitivity index (OSI). Given the increasing interest in individualized and patient-friendly ART approaches, this study aims to compare the efficacy of MPA-based PPOS and GnRH antagonist protocols in terms of oocyte maturation and fertilization outcomes in PCOS women undergoing ICSI cycles.

2. Patients and Methods

This study was designed as a prospective, randomized, open-label, controlled clinical trial conducted at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, Baghdad, Iraq, between 2023 and 2024. Ethical approval was obtained from the institutional review board, and written informed consent was secured from all participants. A total of 108 infertile women diagnosed with polycystic ovary syndrome (PCOS) were enrolled according to the Rotterdam criteria [1]. Inclusion required at least two of the following: oligo/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian

morphology on ultrasound. Inclusion Criteria (Women aged 20–38 years ,Diagnosis of PCOS ,BMI between 18 and 35 kg/m² ,Basal FSH <10 mIU/mL , Both ovaries present , Normal uterine cavity).Exclusion Criteria (Presence of endometriosis, uterine abnormalities, or hydrosalpinx ,Severe male factor infertility , Previous poor ovarian response (≤ 3 oocytes retrieved) ,Known systemic illness or endocrine disorders other than PCOS .Patients were randomized into two equal groups using a computer-generated sequence: Group I (PPOS group; n=49): Received oral Medroxyprogesterone Acetate (MPA) 10 mg/day from cycle day 2 until the day of ovulation trigger. Group II (GnRH antagonist group; n=59): Underwent a flexible GnRH antagonist protocol starting when the lead follicle reached ≥ 14 mm, with daily subcutaneous cetrorelix acetate 0.25 mg.All patients received human menopausal gonadotropin (HMG) injections (150–225 IU/day), starting on day 2 of the menstrual cycle. Gonadotropin doses were adjusted individually based on ovarian reserve markers (antral follicle count and AMH levels) and follicular growth monitored by transvaginal ultrasound (TVUS).Hormonal assessments (FSH, LH, estradiol, testosterone) were performed on days 2, 6, and the trigger day. Ovulation was triggered with 250 μ g recombinant human chorionic gonadotropin (hCG) when at least three follicles reached ≥ 18 mm. In both groups, transvaginal oocyte retrieval was performed 36 hours post-trigger.Collected cumulus-oocyte complexes were denuded and evaluated for nuclear maturity. Mature metaphase II (MII) oocytes underwent ICSI. Fertilization was confirmed by the presence of two pronuclei (2PN) 16–18 hours later. Embryos were cultured and graded on Day 3 based on cell number, fragmentation, and symmetry: Grade 1: ≥ 7 cells, no fragmentation ,Grade 2: ≥ 6 cells, <20% fragmentation ,Grade 3: <6 cells or >20% fragmentation .All embryos were cryopreserved to avoid fresh transfer due to potential endometrial asynchrony in the PPOS group. Outcome Measures ,Number of oocytes retrieved ,Fertilization rate

(number of 2PN / number of injected oocytes) Number of MII oocytes ,Embryo quality (Day 3 grading) ,Ovarian Sensitivity Index (OSI = [number of retrieved oocytes / total gonadotropin dose] × 1000) ,LH profile across stimulation (Days 2, 6, and trigger day)

3. Results

A total of 108 women with PCOS undergoing ICSI were included in the final analysis: 49 in the Medroxyprogesterone Acetate (MPA) group and 59 in the GnRH antagonist group. There were no significant differences in baseline characteristics between the two groups (Table 1). The mean age was 29.45 ± 5.12 years in the MPA group and 29.29 ± 5.26 years in the antagonist group ($p > 0.05$). Body mass index (BMI) was also comparable (28.47 ± 4.22 vs. 28.16 ± 4.07 kg/m²; $p > 0.05$).

Table (1): Baseline characteristics of participants in the MPA and GnRH antagonist groups

Variable	MPA Group (n=49)	GnRH Antagonist Group (n=59)	p-value
Age (years)	29.45 ± 5.12	29.29 ± 5.26	0.89
BMI (kg/m ²)	28.47 ± 4.22	28.16 ± 4.07	0.76

There were no statistically significant differences in baseline or stimulated hormonal levels between groups. On day 6 and the trigger day, serum LH and estradiol (E2) levels remained effectively suppressed in both protocols (Table 2).

Table (2): Hormonal levels on trigger day

Hormone	MPA Group	GnRH Antagonist Group	p-value
LH (mIU/mL)	1.76 ± 0.30	1.76 ± 0.34	0.99
E2 (pg/mL)	2035.93 ± 656.74	1349.29 ± 360.85	0.07
Testosterone (ng/mL)	No significant difference	—	>0.05

The MPA group showed a numerically higher mean number of retrieved oocytes (20.65 ± 7.50) compared to the antagonist group (13.39 ± 4.41), though the difference did not reach statistical significance ($p = 0.083$). The number of metaphase II (MII) oocytes was also higher in the MPA group (Table 3). The ovarian sensitivity index (OSI) was equivalent between groups.

Table (3): Oocyte retrieval and maturation outcomes

Parameter	MPA Group	GnRH Antagonist Group	p-value
Retrieved oocytes	20.65 ± 7.50	13.39 ± 4.41	0.083
MII oocytes	15.10 ± 5.20	11.24 ± 4.12	0.09
OSI	1.36 ± 0.65	1.36 ± 0.65	0.92

Total doses of HMG and duration of stimulation were not significantly different between the two groups (Table 4).

Table (4): Gonadotropin usage and stimulation days

Parameter	MPA Group	GnRH Antagonist Group	p-value
Total HMG (FSH + LH IU)	1207.5 ± 3.5	1185 ± 3.4	0.66
Stimulation days	9.81 ± 1.0	8.9 ± 1.2	0.07

Fertilization rates, cleavage rates, and embryo quality were comparable across both groups. The number of grade 1 embryos was higher in the MPA group, although differences were not statistically significant (Table 5).

Table (5): Embryological outcomes

Parameter	MPA Group	GnRH Antagonist Group	p-value
Fertilization rate (%)	72.4 ± 10.6	71.2 ± 11.3	0.68
Grade 1 embryos (Day 3)	5.1 ± 2.3	4.6 ± 2.1	0.71
Grade 2 embryos	3.2 ± 1.8	3.0 ± 1.6	0.65
Grade 3 embryos	2.1 ± 1.4	2.5 ± 1.7	0.46

LH levels measured on stimulation days 2, 6, and the trigger day remained consistently suppressed in both protocols, with no premature ovulation or cycle cancellation in either group. There were no significant differences in LH trends at any time point ($p > 0.05$).

4. Discussion

The present study aimed to compare the efficacy of two LH suppression strategies—Medroxyprogesterone Acetate (MPA) as part of a progestin-primed ovarian stimulation (PPOS) protocol versus a flexible GnRH antagonist protocol—on oocyte yield and fertilization outcomes in PCOS women undergoing ICSI cycles. The results suggest that both protocols are effective in suppressing premature LH surge and supporting favorable embryological outcomes, with no significant differences in fertilization rate or ovarian sensitivity index (OSI). Although the MPA group exhibited a numerically higher number of oocytes retrieved and mature metaphase II (MII) oocytes, the difference was not statistically significant. Our findings are consistent with previous studies suggesting that MPA-based PPOS protocols are non-inferior to GnRH antagonists in terms of oocyte maturation and embryo development in PCOS patients [1,2]. The lack of significant differences in oocyte quality and fertilization rate is also supported by Yarali et al. [3], who reported comparable embryological outcomes with MPA and antagonist protocols in hyper-responder women. A notable observation in our study was the trend toward a higher oocyte yield in the MPA group, which aligns with findings by Chen et al. [4] and Zhou et al. [5], who reported increased follicular recruitment under progestin-based suppression. This may be attributed to MPA's indirect, steady modulation of the hypothalamic–pituitary–gonadal axis, resulting in smoother estradiol profiles and more consistent folliculogenesis. Effective prevention of premature LH surges was achieved in both groups, without any cases of spontaneous ovulation or cycle cancellation. LH profiles remained consistently suppressed throughout stimulation, which reaffirms the reliability of both protocols in maintaining pituitary suppression. Previous work has shown that MPA induces negative feedback through the hypothalamus and pituitary, suppressing GnRH pulsatility and thereby LH secretion [6]. GnRH antagonists, in

contrast, block pituitary receptors directly and more rapidly, offering flexibility in LH control [7]. Although both approaches resulted in similar LH values on trigger day, MPA was associated with more stable hormonal dynamics, which may be advantageous in certain patient populations. Lu et al. [8] emphasized that the gradual suppression achieved with oral MPA may reduce hormonal fluctuations and possibly enhance endometrial synchrony in subsequent frozen-thawed embryo transfer cycles. The ovarian sensitivity index (OSI), an emerging marker of ovarian responsiveness, was similar in both groups, indicating that MPA and GnRH antagonist protocols offer comparable efficiency in follicular recruitment relative to the amount of gonadotropin used. This finding supports prior studies suggesting that progestin co-treatment does not impair ovarian response or require significantly altered gonadotropin dosages [9]. Interestingly, stimulation duration and gonadotropin consumption were also comparable between the two groups. This finding differs slightly from that of Zhu et al. [10], who reported a slightly shorter stimulation duration in antagonist protocols. In our trial, the near-equivalence may reflect standardized stimulation thresholds used for PCOS women, mitigating variations between protocols. Embryo cleavage and morphology on Day 3 did not differ significantly between groups. Fertilization rates were similar, supporting the hypothesis that the LH suppression technique does not significantly influence fertilization potential when adequate oocyte maturity is achieved. These findings are supported by Macedo et al. [11], who concluded that embryo quality is more closely related to intrinsic oocyte competence and laboratory handling rather than COS protocol alone. Although the MPA group had numerically higher grade 1 embryos, the lack of statistical significance mirrors similar studies by Roque et al. [12], who found marginally improved embryo morphology in PPOS protocols but without conclusive differences in pregnancy rates.

From a logistical perspective, oral MPA offers several practical benefits: easier administration, improved patient compliance, and reduced treatment costs, especially in resource-limited settings. In countries where daily injections represent a psychological or financial burden, oral suppression may increase ART accessibility [13]. However, the necessity of a freeze-all strategy due to the potential impact of MPA on endometrial receptivity remains a consideration. Studies have shown that progestin exposure during the follicular phase impairs endometrial implantation potential, requiring all embryos to be cryopreserved and transferred in a subsequent natural or hormonally prepared cycle [14]. Furthermore, the lack of fresh transfer makes immediate pregnancy outcomes less assessable in MPA-based studies. Although frozen-thawed cycles are generally associated with improved endometrial receptivity, they delay time to pregnancy and add cryopreservation-related costs [15]. Despite the robust design, our study has limitations. First, the sample size, although adequate to detect major differences, may have been underpowered to detect subtle differences in embryo morphology or OSI. Second, clinical pregnancy and live birth rates were not assessed due to the freeze-all strategy employed for both groups. Future research with follow-up into pregnancy outcomes is warranted. Additionally, while our study focused on high-responder PCOS women, results may not be generalizable to normo-responders or women with diminished ovarian reserve. This study adds to the growing body of evidence supporting the use of progestin-based suppression in controlled ovarian stimulation for ART. The MPA-based PPOS protocol appears to offer a cost-effective, well-tolerated, and equally efficacious alternative to GnRH antagonist protocols in terms of oocyte yield and fertilization outcomes in PCOS patients. Given the similar embryological outcomes, the choice between MPA and antagonist protocols can be guided by factors such as patient preference, cost, compliance potential, and clinic infrastructure. Clinicians should also consider

whether immediate fresh embryo transfer is desired, in which case GnRH antagonists may be preferable

5.Conclusion

This study demonstrates that Medroxyprogesterone Acetate (MPA) as part of a progestin-primed ovarian stimulation (PPOS) protocol is a clinically effective and safe alternative to the conventional GnRH antagonist protocol for the suppression of premature luteinizing hormone (LH) surge in PCOS women undergoing intracytoplasmic sperm injection (ICSI) cycles. Both protocols were equally effective in preventing premature ovulation and maintaining hormonal suppression throughout stimulation. While not statistically significant, a trend toward higher oocyte yield and metaphase II oocyte count was observed in the MPA group, with comparable fertilization rates and embryo quality. Gonadotropin dosage, stimulation duration, and ovarian sensitivity index (OSI) were similar in both groups, indicating that the mode of LH suppression does not adversely affect the efficiency of controlled ovarian stimulation in high-responder PCOS patients. The oral administration, cost-effectiveness, and favorable tolerability of MPA make it an attractive protocol choice, particularly in low-resource or high-volume ART settings. However, the necessity for a freeze-all approach due to possible impairment of endometrial receptivity remains a consideration, warranting careful planning of the embryo transfer strategy.

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Author Contribution

Zahraa Ali performed the study; Muayad Sraibet Abood and Mufeda Ali Jwad supervised the work.

Conflict of Interest

The authors declare no conflict of interest .

Ethical Clearance

The Ethical Approval Committee approved the study.

Financial Disclosure

There is no financial disclosure.

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