ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 8, Issue – 6, November - 2025, Page No.: 23 – 28

Effect of OCP Exposure on Ovulation Success Among Women Undergoing Letrozole-Induced Ovulation Induction in Two different regimens in infertile PCOS Female

[1]Dr. Priyanka Sharma, 3rd Year Postgraduate, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur, Rajasthan, 302007

[2]Dr. Rajani Nawal, Professor, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur, Rajasthan, 302007

[3]Dr. Garima Vyas, Professor, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur, Rajasthan, 302007

[4]Dr. Sanju Khichar, Junior Resident, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur, Rajasthan, 302007

[5]Dr. Pinky Seervi, Junior Resident, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur, Rajasthan, 302007

[6]Dr. Asha Verma, Senior Professor and Unit Head, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur, Rajasthan

Corresponding Author: Dr. Asha Verma, Senior Professor and Unit Head, Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur, Rajasthan.

How to citation this article: Dr. Priyanka Sharma, Dr. Rajani Nawal, Dr. Garima Vyas, Dr. Sanju Khichar, Dr. Pinky Seervi, Dr. Asha Verma, "Effect of OCP Exposure on Ovulation Success Among Women Undergoing Letrozole-Induced Ovulation Induction in Two different regimens in infertile PCOS Female", IJMACR- November - 2025, Volume – 8, Issue - 6, P. No. 23 – 28.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: Polycystic ovary syndrome (PCOS) is a leading cause of anovulatory infertility, and optimizing ovulation induction strategies remains a key challenge in improving reproductive outcomes.

Methods: A randomized controlled trial was conducted in the Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur, from October 2023 to October 2024. A total of 148 infertile women with PCOS (Rotterdam criteria) unresponsive to 2.5 mg letrozole were randomized into two groups: Group 1 received the conventional letrozole regimen (5 mg/day for 5 days), and Group 2 received the extended regimen (5 mg/day for 10 days). Ovulation was monitored by transvaginal

ultrasonography, and outcomes were compared based on prior OCP use. Data were analysed using SPSS v26 with a significance threshold of $p < 0.05$.

Results: The extended regimen achieved a higher ovulation rate (91.89%) compared with the conventional regimen (70.27%) ($p = 0.0005$). Among women with prior OCP use, ovulation occurred in 100% of cases (28/28 in the conventional group and 38/38 in the extended group). In contrast, among non-OCP users, ovulation occurred in 65.9% of participants. Statistical analysis revealed a strong association between prior OCP exposure and ovulatory success ($\chi^2 = 25.61$, $p < 0.001$), with an odds ratio (OR) of 69.55 (95% CI: 3.95–1224.2).

Conclusion: OCP pretreatment significantly enhances ovulation success in infertile PCOS women undergoing letrozole-induced ovulation, particularly with extended dosing. The combination of short-term OCP exposure followed by extended letrozole therapy appears to improve follicular responsiveness and may represent a more effective, evidence-based strategy for managing letrozole-resistant PCOS cases.

Keywords: Polycystic Ovary Syndrome, Letrozole, Oral Contraceptive Pills, Ovulation Induction, Infertility, Extended Regimen

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder and a leading cause of anovulatory infertility worldwide. Letrozole has surpassed clomiphene citrate as the preferred first-line ovulation-induction agent because it yields higher ovulation and live-birth rates with fewer multiple pregnancies[1,2]. Nevertheless, response to letrozole remains inconsistent, suggesting that pretreatment and dosing strategies may influence outcomes.

Combined oral contraceptive (OCP) pretreatment is often used before ovulation induction to schedule cycles and transiently suppress luteinizing hormone (LH) and androgen levels, theoretically improving follicular synchronization. However, data regarding its impact on fertility outcomes are conflicting. Randomized trials in women with PCOS undergoing IVF have shown that OCP pretreatment does not significantly improve embryo quality, pregnancy rate, or live-birth outcomes[3]. Some non-ART studies likewise found no improvement in ovulation or conception rates when OCP pretreatment preceded letrozole induction [3].

The regimen of letrozole itself—dose and duration—also influences ovulatory success. Beyond the standard 2.5–5 mg for 5 days, extended-duration or "stair-step" regimens, which escalate the dose without inducing withdrawal bleeding, have achieved higher ovulation rates and shorter time-to-ovulation, particularly in letrozole-resistant women[4–7] Current international PCOS guidelines endorse individualized approaches but recognize the lack of consensus on optimal pretreatment and regimen protocols [8-10.]

Given these uncertainties, this study aims to evaluate whether OCP pretreatment affects ovulation success among infertile women with PCOS undergoing letrozole-induced ovulation, comparing two evidence-based regimens. Clarifying this interaction may help refine induction protocols, reduce treatment duration, and improve fertility outcomes in this population [9].

Materials and Methods

This interventional randomized controlled trial was conducted in the Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur, to compare the efficacy of extended versus conventional letrozole regimens for ovulation induction in infertile women with

polycystic ovary syndrome (PCOS). Following ethical approval, data collection began in October 2023 and continued for one year.

Infertile women aged 18–40 years diagnosed with PCOS (Rotterdam criteria) who had inadequate response to 2.5 mg letrozole were included. Eligibility required at least one patent fallopian tube, a normozoospermic partner, and an active marital life of three to five years.

Women with endometriosis, thyroid or prolactin disorders, or uterine anomalies were excluded.

Based on 80% power and a 5% significance level, assuming a 20% improvement in ovulation rate with the extended regimen (reference: Zhu et al., 2023), 74 participants were enrolled per group to account for attrition. After informed consent and baseline evaluation—including clinical history, examination, and day 2–3 transvaginal ultrasonography—participants were randomized into two groups.

Group 1 (Conventional Regimen): Letrozole 5 mg/day from day 2–6 for five days.

Group 2 (Extended Regimen): Letrozole 5 mg/day from day 2–11 for ten days.

Follicular monitoring started on day 10. When a follicle ≥18 mm and endometrium ≥7 mm was observed, ovulation was triggered with β-hCG (5,000–10,000 IU) followed by intrauterine insemination (IUI) after 36 hours and luteal phase progesterone support. Ovulation was confirmed by follicular rupture on ultrasound and pregnancy by serum β-hCG >50 mIU/mL and fetal cardiac activity on scan.

Data were analysed using SPSS v26. Continuous variables were expressed as mean ± SD and compared using Student's t-test; categorical variables were compared using Chi-square or Fisher's exact test. A p-value <0.05 was considered statistically significant.

Results

Among the 148 infertile women with PCOS enrolled in the study, demographic characteristics were broadly comparable between groups. The largest proportion of participants (45.3%) were aged 28–32 years, followed by 30.4% in the 37–40-year range and 24.3% between 33 and 36 years. Most women (69.6%) had a normal body mass index (BMI) of 18.5–22.9 kg/m², while 30.4% were overweight (BMI ≥23 kg/m²). Primary infertility was predominant, reported in 89.9% of cases, whereas 10.1% had secondary infertility. The duration of active marital life (AML) exceeded three years in 70.3% of participants. A smoking history was present in 20.3% of cases, prior oral contraceptive pill (OCP) use in 44.6%, and clinical signs of hyperandrogenism in 22.3% of the study population.

In terms of ovulation outcomes, the extended letrozole regimen demonstrated a significantly higher ovulation rate than the conventional regimen. Ovulation occurred in 68 out of 74 participants (91.89%) in the extended group compared with 52 out of 74 (70.27%) in the conventional group, a difference that was statistically significant ($p = 0.0005$).

Further analysis examined the effect of prior OCP use on ovulation success across both regimens. Among women with a history of OCP use, ovulation occurred in 28 (42.42%) participants in the conventional group and 38 (57.58%) in the extended group, with no cases of anovulation in either subgroup. In contrast, among those without prior OCP exposure, ovulation failure occurred in 22 (26.83%) women in the conventional regimen and 6 (7.32%) in the extended regimen, whereas ovulation was achieved in 24 (29.27%) and 30 (36.59%) participants, respectively.

The statistical analysis revealed a strong and significant association between prior OCP exposure and ovulation success. The chi-square test yielded a value of 25.61 with a p-value of <0.001, confirming high statistical significance. The calculated odds ratio (OR) was 69.55, with a 95% confidence interval (Haldane correction) ranging from 3.95 to 1224.2, indicating that women with prior OCP exposure had markedly higher odds of successful ovulation compared to those without. This finding suggests that OCP pretreatment may enhance follicular responsiveness to letrozole, particularly in the extended regimen.

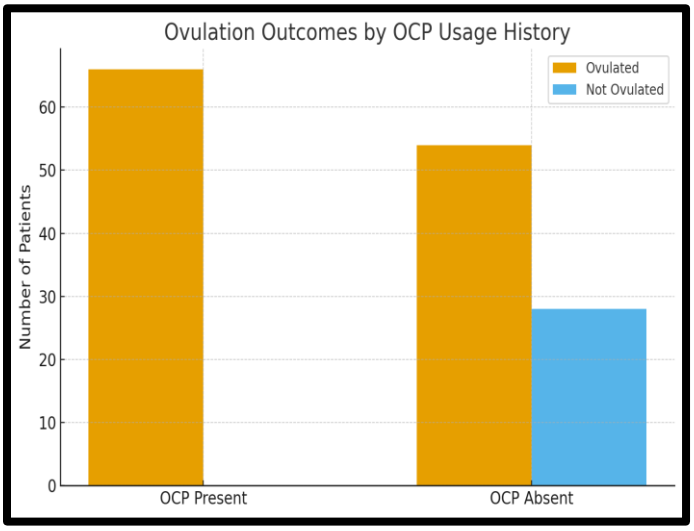
Table 1: Effect of Prior Oral Contraceptive Pill (OCP) Usage on Ovulation Outcomes in Conventional and Extended Letrozole Therapy

OCP Usage	Conventional Group – No Ovulation	Conventional Group – Ovulation	Extended Group – No Ovulation	Extended Group – Ovulation	Total
Present	0 (0.00%)	28 (42.42%)	0 (0.00%)	38 (57.58%)	66 (44.59%)
Absent	22 (26.83%)	24 (29.27%)	6 (7.32%)	30 (36.59%)	82 (55.41%)
Total	22 (14.86%)	52 (35.14%)	6 (4.05%)	68 (45.95%)	148 (100.00%)

Table 2: Association of Prior OCP Use with Ovulation Outcomes

Statistic	Value
Chi-square (χ^2)	25.61
p-value	< 0.001
Odds Ratio (OR)	69.55
95% CI (Haldane correction)	3.95 – 1224.2
Interpretation	Strong, statistically significant association

Figure 1: Ovulation outcomes by OCP Usage history



Discussion

This randomized controlled trial evaluated the effect of prior oral contraceptive pill (OCP) exposure on ovulation outcomes in infertile women with polycystic ovary syndrome (PCOS) undergoing letrozole-induced ovulation using two dosing regimens—conventional and extended. The findings revealed that the extended letrozole regimen achieved a significantly higher ovulation rate (91.89%) compared with the conventional regimen (70.27%), and prior OCP exposure was strongly associated with ovulatory success (OR = 69.55; 95% CI: 3.95–1224.2; p< 0.001). These results suggest that OCP pretreatment may enhance ovarian responsiveness to letrozole, particularly when used with an extended regimen.

The findings of this study are consistent with previous literature emphasizing the benefits of OCP pretreatment in PCOS. OCPs transiently suppress the hypothalamic–

pituitary–ovarian axis, reduce luteinizing hormone (LH) hypersecretion, and lower androgen levels, leading to improved follicular synchronization and a more coordinated ovulatory response during subsequent induction cycles[3,4]. Gao et al.[3] reported that short-term OCP pretreatment before controlled ovarian stimulation normalized LH/FSH ratios and improved follicular growth dynamics. Similarly, the 2023 International PCOS Guideline highlights that short-term hormonal suppression can be advantageous in selected cases of hyperandrogenic or treatment-resistant PCOS[4].

Letrozole remains the preferred first-line ovulation induction agent, outperforming clomiphene citrate in both ovulation and live-birth rates[6]. Franik et al.[6] demonstrated in a Cochrane meta-analysis that aromatase inhibitors offer superior outcomes compared with clomiphene, especially in women with letrozole resistance or suboptimal response. The present findings extend this evidence by indicating that pre-treatment with OCPs may further optimize the hormonal environment for letrozole responsiveness.

The superiority of the extended regimen aligns with studies by Zhu and Fu[4] and Mandelbaum et al.[7], who observed higher ovulation rates with prolonged or "stair-step" letrozole protocols compared to conventional 5-day regimens. Prolonged aromatase inhibition extends follicular stimulation, sustains intraovarian androgen levels necessary for FSH sensitivity, and facilitates the selection of a dominant follicle[4,7]. Thomas et al.[5] similarly demonstrated improved ovulatory outcomes using sequential or extended letrozole protocols in clomiphene-resistant PCOS cases.

The combined effect of OCP pretreatment followed by extended letrozole therapy likely results from hormonal "resetting"—the OCP phase suppresses androgen excess and follicular asynchrony, while the extended letrozole phase provides adequate time for follicular recruitment and maturation. This dual-phase approach appears particularly effective in women with prior resistance to ovulation induction.

However, this study's limitations should be acknowledged. It focused primarily on ovulation rates and did not assess clinical pregnancy or live-birth outcomes, which are essential for establishing true therapeutic efficacy. Moreover, metabolic and hormonal confounders such as insulin resistance, fasting insulin levels, or baseline androgen status were not evaluated, which may influence treatment response. Future studies incorporating endocrine and metabolic profiling pre- and post-OCP exposure are warranted to delineate the exact mechanisms underlying the observed improvement in ovulatory outcomes.

Conclusion

Prior OCP exposure significantly enhances ovulation success in infertile PCOS women undergoing letrozole-induced ovulation, especially with extended dosing. The integration of short-term OCP pretreatment followed by extended letrozole therapy represents a promising, evidence-based approach to optimize ovulation induction in resistant PCOS patients and could serve as a practical modification in standard infertility management protocols.

References

1. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, et al. 'Letrozole versus clomiphene for infertility in the polycystic ovary syndrome', New England Journal of Medicine, 2014, 371(2), pp. 119–129. doi: 10.1056/ NEJMoa 1313517.

2. Teede HJ, Tay CT, Laven J, Dokras A, Moran LJ, Piltonen TT, et al., 'Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome', Journal of Clinical Endocrinology & Metabolism, 2023, 108(10), pp. 2447–2469. doi: 10.1210/clinem/dgad496.
3. Gao J, Mai Q, Zhong Y, Miao B, Chen M, Luo L, et al., 'Pretreatment with oral contraceptive pills in women with PCOS scheduled for IVF: a randomized clinical trial', Human Reproduction Open, 2024, 2024(2), hoae019. doi: 10.1093/hropen/hoae019.
4. Zhu X and Fu Y, 'Extending letrozole treatment duration is effective in inducing ovulation in women with polycystic ovary syndrome and letrozole resistance', Fertility and Sterility, 2023, 119(1), pp. 107–113. doi: 10.1016/j.fertnstert.2022.09.018.
5. Thomas S, Woo I, Ho J, Jones T, Paulson R, Chung K, et al., 'Ovulation rates in a stair-step protocol with letrozole vs clomiphene citrate in patients with polycystic ovarian syndrome', Contraception and Reproductive Medicine, 2019, 4, p. 20. doi: 10.1186/s40834-019-0102-4.
6. Franik S, Eltrop SM, Kremer JA, Kiesel L and Farquhar C, 'Aromatase inhibitors (letrozole) for ovulation induction in infertile women with polycystic ovary syndrome', Cochrane Database of Systematic Reviews, 2022, 10, CD010287. doi: 10. 1002/14651858.CD010287.pub3.
7. Mandelbaum RS, Agarwal R, Melville S, Violette CJ, Winer S, Shoupe D, et al., 'A comparison of letrozole regimens for ovulation induction in women with polycystic ovary syndrome', F&S Reports, 2024, 5(2), pp. 170–175. doi: 10.1016/ j.xfre. 2024. 03.004.
8. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al., 'Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome (2018)', Human Reproduction, 2018, 33(9), pp. 1602–1618. doi: 10.1093/humrep/dey256.
9. Katler Q and Verrilli L, 'Patience and persistence: is duration the missing piece for treating polycystic ovary syndrome resistance?', Fertility and Sterility, 2023, 119(1), pp. 114–115. doi: 10.1016/ j.fertnstert. 2022.11.008.
10. Teede HJ, Tay CT, Laven J, Dokras A, Moran LJ, Piltonen TT, et al., 'The 2023 International Guideline for the Assessment and Management of PCOS—summary article', Human Reproduction, 2023, 38(9), pp. 1655–1679. doi: 10.1093/ humrep/ dead156.