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ORIGINAL ARTICLE

Comparative Effectiveness of Letrozole Alone versus Letrozole Plus Oradexon in Ovulation Induction Among Rural Women with PCOS: A Retrospective Analysis of 60 Positive Pregnancies

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ABSTRACT

Background: *Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder and the leading cause of anovulatory infertility among reproductive-aged women. Letrozole is currently recommended as first-line ovulation induction therapy; however, adjunctive glucocorticoids have been proposed to enhance ovarian response, particularly in hyperandrogenic populations. This study aimed to compare the effectiveness of letrozole alone versus letrozole combined with oradexon for ovulation induction among rural women with PCOS.* ***Methods & Materials:*** *This retrospective comparative study was conducted at Jahurunessa Hospital, Rupganj, Narayanganj, from June 2024 to May 2025. Sixty women diagnosed with PCOS based on Rotterdam criteria were included in this study. Participants underwent ovulation induction with either letrozole alone (n = 36) or letrozole plus oradexon (n = 24). Baseline demographic, hormonal and ultrasonographic parameters, follicular response, endometrial thickness, ovulation and pregnancy outcomes were analyzed using SPSS version 25.0.* ***Results:*** *Baseline characteristics, hormonal profiles, PCOS phenotypes and ovarian reserve markers were comparable between groups. The combination therapy group demonstrated a significantly higher mean number of mature follicles (≥18 mm) at trigger compared with the letrozole-alone group (1.92 ± 0.65 vs. 1.19 ± 0.47; p < 0.001).* Endometrial thickness at trigger was higher in combination therapy (10.08±1.57 vs 10.92±1.25; p=0.032). *However, ovulation rates, pregnancy rates and clinical pregnancy rates did not differ significantly between groups.* ***Conclusion:*** *Although the addition of oradexon to letrozole significantly enhanced follicular response, it did not translate into improved ovulation or pregnancy outcomes. Letrozole monotherapy remains an effective, safe and practical first-line ovulation induction strategy for rural women with PCOS.*

Keywords: *Polycystic ovary syndrome, Letrozole, Dexamethasone, Infertility*

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age and represents a leading cause of anovulatory infertility worldwide.[1,2] Characterized by ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology, PCOS exhibits considerable phenotypic heterogeneity, with prevalence estimates ranging from 6% to 20% depending on diagnostic criteria and population studied.[3,4] In low- and middle-income countries, particularly in rural settings, delayed diagnosis and limited access to fertility services further exacerbate reproductive morbidity associated with the disorder.[5]

Ovulation induction remains the cornerstone of infertility management in women with PCOS. Aromatase inhibitors, particularly letrozole, have emerged as first-line agents owing to superior ovulation and live birth rates compared with clomiphene citrate and a more favorable endometrial profile.[6,7] Letrozole acts by inhibiting estrogen synthesis, leading to increased gonadotropin secretion and subsequent follicular development without prolonged anti-estrogenic effects on the endometrium.[8] Consequently, international guidelines now recommend letrozole as the preferred initial therapy for anovulatory infertility in PCOS.[9]

Despite its effectiveness, a subset of women demonstrates suboptimal follicular response or resistance to letrozole monotherapy. Adjunctive therapies aimed at enhancing ovarian responsiveness have therefore been explored. Glucocorticoids such as dexamethasone have been proposed as potential adjuvants due to their ability to suppress adrenal

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androgen production, improve follicular sensitivity to gonadotropins and modulate intra-ovarian hormonal milieu.[10,11] Previous randomized and observational studies suggest that combining letrozole with glucocorticoids may increase follicular recruitment and ovulation rates, particularly in hyperandrogenic or letrozole-resistant PCOS populations.[12,13]

However, evidence regarding the clinical benefit of combination therapy remains inconsistent. While some trials report improved follicular response and pregnancy outcomes, others demonstrate no significant advantage over letrozole alone, raising questions about patient selection, safety and cost-effectiveness.[14,15] Moreover, data from rural populations are scarce, where socioeconomic factors, nutritional status and healthcare access may influence treatment outcomes differently from urban or tertiary-care settings.

OBJECTIVES

The objective of this study was to compare the effectiveness of letrozole alone versus letrozole combined with oradexon for ovulation induction among rural women with PCOS.

METHODS & MATERIALS

This retrospective comparative study was conducted at Jahurunessa Hospital, Rupganj, Narayanganj, Bangladesh, from June 2024 to May 2025. This study included 63 reproductive-aged women diagnosed with polycystic ovary syndrome (PCOS) who underwent letrozole-based ovulation induction and subsequently achieved pregnancy. Three patients dropped out of the study; therefore, the final sample size was 60. All participants were residents of rural communities surrounding the hospital and were managed through the hospital's infertility clinic, following standardized diagnostic and treatment protocols.

Selection Criteria

Inclusion Criteria: This study included women aged 18–35 with PCOS-related anovulatory infertility who achieved a biochemical or clinical pregnancy following letrozole ovulation induction.

Exclusion Criteria: Participants with tubal pathology, male-factor infertility, significant endocrine or metabolic disorders, or concurrent use of other ovulation-induction agents.

Data Collection Procedure

Data collection followed a structured and standardized protocol to ensure completeness and consistency across all cases. At enrollment, each participant underwent a comprehensive clinical evaluation that included detailed reproductive history, menstrual patterns and previous infertility treatments. Anthropometric measurements such as height, weight and BMI were recorded. A baseline hormonal assessment was performed on days 2–3 of the menstrual cycle, including serum FSH, LH and AMH levels, as well as a clinical evaluation for hyperandrogenism. Transvaginal ultrasonography was conducted to document antral follicle count, ovarian morphology and baseline endometrial thickness using a standardized imaging protocol.

All participants initially received oral letrozole at a dose of 5 mg/day or 7.5 mg/day for five consecutive days starting on cycle day 2. Dose selection was individualized based on body mass index, ovarian reserve markers and prior response to ovulation induction. Women who failed to demonstrate an adequate follicular response to letrozole alone were defined as absence of a dominant follicle measuring ≥18 mm on serial ultrasonography and who exhibited clinical or biochemical hyperandrogenism were subsequently managed with combination therapy. This regimen consisted of letrozole at the same individualized dose plus oral oradexon (dexamethasone) 0.5 mg once daily administered during the follicular phase. Follicular monitoring was performed through serial ultrasonography beginning on cycle days 9-10, with tracking of dominant follicle development, endometrial changes and timing of ovulation trigger when indicated. Data on treatment cycles, number of mature follicles, ovulation confirmation and administration of hCG trigger injections were recorded. Pregnancy outcomes including biochemical pregnancy, clinical pregnancy on ultrasound and early complications were documented during follow-up visits. Informed consent was obtained from all participants after explaining the study objectives, procedures and confidentiality safeguards. The study adhered to the principles of the Declaration of Helsinki.

Statistical Analysis

Data analysis was performed using SPSS version 25.0. Descriptive statistics summarized demographic, hormonal and treatment variables using means, standard deviations, frequencies and percentages. Inferential statistics, including median and interquartile ranges, were applied where appropriate. P value <0.05 considered as statistically significant.

RESULTS

Table I presents the baseline demographic and clinical characteristics of participants according to treatment group. The mean age was significantly lower in the letrozole-alone group compared with the letrozole plus oradexon group (22.2 ± 2.7 vs. 25.3 ± 2.8 years; $p < 0.001$). Mean body mass index was comparable between groups (26.4 kg/m^2 in both groups; $p = 0.747$). Primary infertility was more frequent among women receiving letrozole alone (66.7%) than those receiving combination therapy (41.7%), although this difference was not statistically significant ($p = 0.099$).

Table – I: Baseline Characteristics of study population (*n*=60)

Characteristic		Letrozole Alone (n=36)	Letrozole+Oradexon (n=24)	p-value
Age (years), mean±SD		22.2±2.7	25.3±2.8	<0.001
BMI (kg/m^2), mean±SD		26.4±1.7	26.4±2.4	0.747
Infertility type, n (%)	Primary	24 (66.7)	10 (41.7)	0.099
	Secondary	12 (33.3)	14 (58.3)	
Duration infertility (years), mean±SD		2.18±1.14	2.75±1.25	0.055
Parity, n (%)	Nulliparous	28 (77.8)	15 (62.5)	0.262
	Multiparous	8 (22.2)	9 (37.5)	

Table II describes the distribution of PCOS phenotypes based on the Rotterdam criteria. Phenotype A was the most prevalent in both groups, accounting for 47.2% in the letrozole-alone group and 66.7% in the combination group. Phenotypes B, C

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and D were less frequently observed across both groups. No statistically significant difference in phenotype distribution was identified between treatment arms (p = 0.175).

Table – II: Distribution of PCOS Phenotypes by Treatment Group (*n*=60)

PCOS Phenotype	Letrozole Alone (n=36) n (%)	Letrozole+ Oradexon (n=24) n (%)	p-value
A	17 (47.2)	16 (66.7)	0.175
B	7 (19.4)	3 (12.5)	
C	2 (5.6)	3 (12.5)	
D	10 (27.8)	2 (8.3)	

A: Oligomenorrhea + Hyperandrogenism + PCOM; B: Oligomenorrhea + Hyperandrogenism; C: Hyperandrogenism + PCOM; D: Oligomenorrhea + PCOM

Table – III: Hormonal and Baseline Ultrasonographic Parameters

Variable	Letrozole Alone (mean ± SD)	Letrozole + Oradexon (mean ± SD)	p-value
AMH (ng/mL)	8.49 ± 1.82	9.14 ± 2.35	0.23
FSH (D2/D3)	5.49 ± 1.51	5.27 ± 1.37	0.56
LH (D2/D3)	11.88 ± 2.21	12.06 ± 2.68	0.77
AFC	21.8 ± 4.6	22.4 ± 5.1	0.63
Baseline endometrial thickness (mm)	5.51 ± 0.47	5.48 ± 0.48	0.81

Table III summarizes baseline endocrine and ultrasonographic parameters. Mean anti-Müllerian hormone levels, follicle-stimulating hormone, luteinizing hormone, antral follicle count and baseline endometrial thickness were comparable between the two groups. No statistically significant differences were observed for any measured parameter.

Table – IV: Distribution of Participants with Mature Follicle and Endometrial Thickness at Trigger (mm)

Parameter	Letrozole Alone (n=36)	Letrozole+Oradexon (n=24)	p-value
Mature follicles (≥18 mm)	1.19±0.47	1.92±0.65	<0.001
Endometrial thickness at trigger (mm)	10.08±1.57	10.92±1.25	0.032

Table IV presents the follicular response and endometrial thickness at the time of ovulation trigger. The mean number of mature follicles (≥18 mm) was significantly higher in the letrozole plus oradexon group compared with the letrozole-alone group (1.92 ± 0.65 vs. 1.19 ± 0.47; p < 0.001). Endometrial thickness at trigger was higher in letrozole plus oradexon group (10.08±1.57 vs 10.92±1.25; p = 0.032).

Table – V: Ovulation, Pregnancy Outcomes

Outcome	Letrozole Alone (n=36) n (%)	Letrozole+Oradexon (n=24) n (%)	p-value
Ovulation achieved	36 (100.0)	24 (100.0)	
Pregnancy achieved	36 (100.0)	24 (100.0)	
Clinical pregnancy	35 (97.2)	24 (100.0)	0.412

Table V outlines ovulation and pregnancy outcomes. Ovulation was achieved in all women receiving letrozole alone and those receiving combination therapy. Pregnancy and clinical pregnancy rates were similar in both groups, with no statistically significant differences observed.

DISCUSSION

The present study evaluated the comparative effectiveness of letrozole alone versus letrozole combined with oradexon for ovulation induction among rural women with PCOS. The findings demonstrate that while baseline demographic, hormonal and ultrasonographic characteristics were largely comparable between groups, combination therapy resulted in a significantly higher number of mature follicles without conferring a statistically significant advantage in ovulation or pregnancy rates.

The similarity in baseline BMI, hormonal parameters and antral follicle count between treatment groups supports the internal validity of the comparison and aligns with prior reports emphasizing the importance of baseline ovarian reserve and endocrine homogeneity when assessing ovulation induction outcomes. Dumont et al. and Karabay Akgul et al. have highlighted that AMH, AFC and gonadotropin levels are key predictors of ovarian responsiveness in PCOS, reinforcing the relevance of comparable baseline profiles in interpreting treatment effects.[16,17]

A notable finding of this study is the significantly higher number of mature follicles observed in the letrozole plus oradexon group. This observation is consistent with reports by Shaheen et al. and Neblett et al. who demonstrated enhanced follicular recruitment with the addition of glucocorticoids, potentially mediated through suppression of adrenal androgen production and improved follicular sensitivity to gonadotropins.[10,11] Hyperandrogenism is known to disrupt folliculogenesis in PCOS and glucocorticoid-induced androgen suppression may partially restore follicular dynamics, explaining the observed increase in mature follicles.

Despite this enhanced follicular response, ovulation and pregnancy rates did not differ significantly between groups. This finding mirrors results from Eskandar et al., as well as Farzaneh and Afshar, who reported that combination strategies may improve intermediate outcomes without translating into superior pregnancy rates.[12,18] These findings suggest that follicle quantity alone may not be the sole determinant of reproductive success and that oocyte quality, endometrial receptivity and luteal function also play critical roles.

Endometrial thickness at trigger was comparable between treatment arms, supporting previous evidence that letrozole preserves endometrial receptivity due to the absence of prolonged anti-estrogenic effects. Wallace et al. demonstrated favorable endometrial gene expression profiles with letrozole compared with clomiphene, a finding that may explain the uniformly high clinical pregnancy rates observed in both groups in the present study.[8] The addition of oradexon did not appear to adversely affect endometrial development, which is clinically reassuring.

The high ovulation and pregnancy rates reported in both groups are consistent with contemporary literature identifying letrozole as an effective first-line agent for ovulation induction in PCOS. Large meta-analyses by Wang et al. and Franik et al. have confirmed superior ovulation and live birth outcomes with letrozole compared with alternative agents, supporting its widespread adoption in clinical practice.[4,6] The lack of additional benefit from oradexon in terms of pregnancy outcomes suggests that routine combination therapy may not be necessary for all patients, particularly in non-resistant populations.

Importantly, the rural context of this study adds valuable insight into fertility management in resource-limited settings. Prior studies have largely been conducted in tertiary or urban centers, whereas socioeconomic and healthcare access factors may influence adherence, monitoring and outcomes in rural populations. The findings suggest that letrozole monotherapy remains an effective and pragmatic approach in such settings, minimizing medication burden and potential side effects.

Overall, this study contributes to the growing body of evidence indicating that while adjunctive therapies may enhance follicular response, they do not necessarily improve reproductive outcomes in unselected PCOS populations. Careful patient selection remains essential when considering combination ovulation induction strategies.

CONCLUSION

Letrozole alone and letrozole combined with oradexon were both highly effective for ovulation induction in rural women with PCOS. Although combination therapy significantly increased mature follicle numbers, it did not improve ovulation or pregnancy outcomes. Letrozole monotherapy remains a reliable and practical first-line option in resource-limited settings.

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Conflicts of interest: There are no conflicts of interest.

Ethical approval: The study was approved by the DMCH.

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