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Evaluating the Efficacy of Letrozole and Letrozole-Dexamethasone Combination in Inducing Ovulation in Women with PCOS-Related Subfertility: An Experimental Study

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Abstract:

Polycystic ovarian syndrome (PCOS) is a major cause of subfertility in women, frequently requiring ovulation induction treatments. This study evaluated the effectiveness of Letrozole alone versus Letrozole plus Dexamethasone in improving ovulation outcomes in women with PCOS-related subfertility. A randomized controlled trial involved 100 participants split into two groups: Group A received Letrozole alone, and Group B received Letrozole with Dexamethasone. Ultrasound was used to assess follicular diameter and endometrial thickness. Results indicated a significantly greater mean follicular diameter (20.70 ± 4.478 vs. 17.54 ± 3.364, $p < .000$) and endometrial thickness (6.84 ± 0.997 vs. 5.92 ± 0.922, $p < .000$) in Group B versus Group A. Dexamethasone appears to enhance ovulation induction by promoting follicular growth and improving endometrial receptivity. The study adds to the evidence supporting the Letrozole-Dexamethasone combination for treating PCOS.

Introduction

Polycystic ovarian syndrome (PCOS) is an endocrine disorder affecting women during their reproductive years, with a global prevalence of roughly 5-10%. Polycystic ovarian morphology is identified through the evaluation of clinical and/or biochemical hyperandrogenism, ovulatory dysfunction, and ultrasound findings of several ovarian cysts. The medical condition defined by the ovaries' inability to release a fertilized ovum is termed ovulatory failure, resulting in an inability to conceive and leading to subfertility (1). PCOS exacerbates subfertility, hence complicating the achievement of successful pregnancies in women (1). The condition is believed to be caused by abnormalities in the female germ cell development within the somatic cells of the ovary and matures into a fertilizable egg, known as folliculogenesis and hormone control (2, 3). PCOS is a medical disorder that can impede female fertility, making conception more difficult. Effective procedures for promoting ovulation are essential to manage this problem. (4). A particular methodology is being employed utilizing various pharmaceuticals for ovulation induction. Letrozole, an aromatase inhibitor developed initially for breast cancer therapy, is now utilized for this indication. Letrozole is more effective than other drugs used to stimulate ovulation in women with PCOS who are struggling with subfertility (5, 6). Unlike other drugs (e.g., clomiphene citrate) used for ovulation induction, Letrozole does not have any antiestrogenic effects on the endometrium or cervical mucus. Consequently, it creates a more favorable uterine environment for fertilizing an egg. However, there is still ongoing controversy regarding the role of adjuvant drugs in enhancing the ovulatory response to Letrozole. Research has been conducted to assess the effectiveness of

the synthetic corticosteroid dexamethasone as an adjunct treatment for managing subfertility in women with PCOS. Dexamethasone inhibits the production of adrenal androgens, substances that interfere with eggs' normal growth and development. Furthermore, it improves insulin sensitivity, which is implicated in the fundamental mechanisms of PCOS (9). Dexamethasone, when combined with various pharmacological treatments, has shown beneficial results in people with PCOS, including increased ovulation, improved fertility, and normalized hormone levels (8). Prior research examining PCOS-associated subfertility used characteristics such as endometrial thickness and follicular diameter while evaluating the effectiveness of Letrozole and Letrozole combined with Dexamethasone in the study cohorts. For subjects taking Letrozole only, the results showed the mean diameter of follicles (mean ± SD = 14.4 ± 2.89) (7) and the Endometrial thickness (mean ± SD = 7.4 ± 2.2) (8). For subjects taking Letrozole + Dexamethasone, the results showed the mean diameter of follicles (mean ± SD = 18.73 ± 3.172) and the Endometrial thickness (mean ± SD = 10.60 ± 1.831) (9). Although these trials convincingly illustrated the advantages of Letrozole + Dexamethasone in enhancing pregnancy rates among PCOS patients, many potential limitations may have affected the non-significant results regarding endometrial thickness and follicular diameter. First, the endometrial thickness p-value (0.11) was close to statistically significant, suggesting that a carefully selected sample size or more sensitive analysis might have revealed a considerable difference. Second, geographical variations in PCOS presentation and response to treatment could have influenced the study's outcomes. Additionally, variations in laboratory techniques or measurement methods used to assess endometrial thickness and follicular diameter could have contributed to the lack of statistical significance. Finally, the study's duration may have been insufficient to capture the full impact of the treatments on these variables, as changes in endometrial thickness and follicular diameter might require a more extended observation period (8). The current study aimed to assess the impact of Letrozole alone and Letrozole in combination with Dexamethasone on ovulation in women experiencing subfertility associated with polycystic ovary syndrome (PCOS). The goal was to evaluate the results of these two treatment protocols in stimulating ovulation by examining the size of follicles and the thickness of the endometrial lining in each treatment group.

Methods

This experimental study was conducted as a randomized controlled trial to assess the efficacy of the Letrozole and Letrozole-Dexamethasone combination in inducing ovulation in women with PCOS-related subfertility. The research was carried out at the Pakistan Institute of Medical Sciences (PIMS), with subjects recruited from the Maternal and Child Healthcare (MCH) OPD during their regular visits for subfertility treatment. All participants provided informed consent, and demographic data were collected before the treatment.

Data Collection Methods

One hundred subjects were recruited and allocated into two groups of fifty individuals each. Group A received Letrozole for 5 days, while Group B received Letrozole for 5 days in conjunction with Dexamethasone for 12 days. An ultrasound was performed, and measurements of follicular diameter and endometrial thickness were recorded. (See Figure 1).

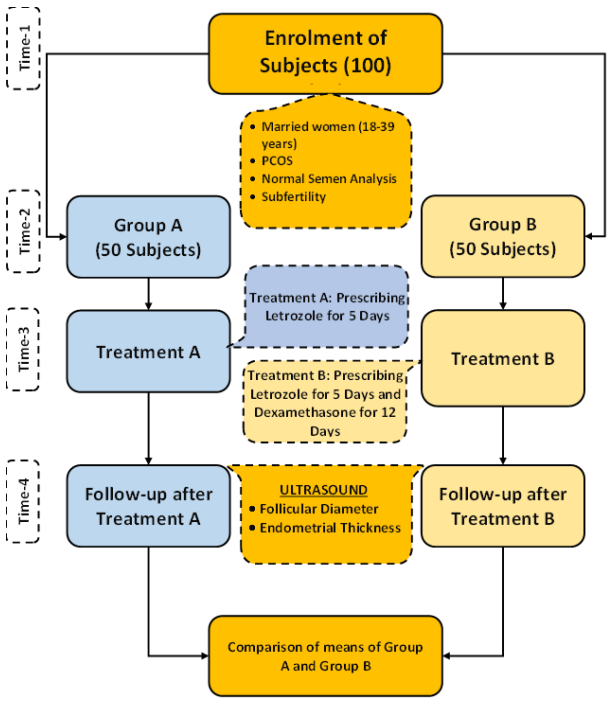

Figure 1: Data Collection Procedures

Inclusion Criteria

The study included married women aged 18–39 years diagnosed with PCOS according to the Rotterdam criteria. Participants were required to have experienced subfertility, defined as the inability to conceive after one year of unprotected intercourse. Additional inclusion criteria included a BMI of 18.5–30 kg/m² and normal thyroid and prolactin levels.

Exclusion Criteria

Women with secondary infertility, endometrial pathologies, or other endocrine disorders, such as hypothyroidism, were excluded. Additionally, participants with a history of ovarian cancer, recent use of fertility medications, or pregnancy-related conditions were not eligible. Women with autoimmune diseases, active infections, or those who were pregnant or breastfeeding were also excluded from the study.

Statistical Analysis

The data collected from the various groups were tabulated and statistically analyzed using suitable statistical tests. Descriptive statistics were applied to summarize demographic and clinical characteristics. The mean follicular size and endometrial thickness were compared using independent samples t-tests. The impact of effect modifiers, including age, BMI, and parity, was also examined. P-value <0.05 was moderately significant, and p-value <0.01 was highly significant. All data analyses were performed using SPSS version 24.

Results

Results of the independent samples t-test showed that the participants were randomly distributed between two groups, i.e., Group-A and Group-B, in terms of their age, BMI, Husband's age, years married for, number of children, last child born, last menstrual period (See Table 1). The results showed that the mean follicular diameter in Group A was 17.54 ± 3.364, and in Group B was 20.70 ± 4.478. The mean difference was statistically significant (t = -3.990, SE Difference = 0.792, p < .000, LLCI = -4.732, ULCI = -1.588). The results also showed that the mean endometrial thickness in Group A was 5.92 ± 0.922, and in Group B was 6.84 ± 0.997. The mean difference was statistically significant (t = -4.789, SE Difference = .192, p < .000, LLCI = -1.301, ULCI = -.539) (See Table 2 and 3).

Table 1: Independent Samples T-test for demographics

	Levene's Test for Equality of Variances		t-test for Equality of Means					
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	LLCI; ULCI
Patient's Age	8.53	.00	-1.92	98	.058	-1.460	.762	-2.973; .053
BMI	9.97	.00	.83	98	.408	.380	.458	-.528; 1.288
Husband's Age	1.86	.18	-1.90	98	.060	-1.780	.935	-3.636; .076
Married for (years)	3.86	.05	-1.84	98	.068	-.900	.488	-1.869; .069
Parity	9.70	.00	1.50	98	.14	.140	.093	-.045; .325
Last Child Born	2.07	.15	.88	98	.38	.340	.386	-.427; 1.107
Last Menstrual Period	.48	.49	-1.13	98	.26	-.960	.848	-2.643; .723

Table 2: Means, Standard Deviation, Standard Error Mean

	Group	N	Mean	Std. Deviation	Std. Error Mean
Follicular Diameter	A	50	17.54	3.364	.476
	B	50	20.70	4.478	.633
Endometrial Thickness	A	50	5.92	.922	.130
	B	50	6.84	.997	.141

Table 3: Independent Samples T-test

	Levene's Test for Equality of Variances		t-test for Equality of Means					
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	LLCI; ULCI
Follicular Diameter	5.43	.02	-3.99	98	.000	-3.16	.79	-4.73; -1.59
Endometrial Thickness	.69	.41	-4.79	98	.000	-.92	.19	-1.30; -0.54

Discussion

This experimental study aimed to compare the efficacy of Letrozole with the combination of Dexamethasone in women with PCOS-related subfertility. The participants' profiles were comparable in Group A and Group B, with no significant difference between age (30.2 versus 31.6 years), BMI (26.4 versus 26.1 kg/m^2), and duration of subfertility (5.1 versus 6.0 years). Our study observed a significant difference in follicular diameter in the group taking Letrozole with Dexamethasone compared to the group taking Letrozole alone. The mean follicular diameter of the participants taking Letrozole and Dexamethasone was higher than those taking

Letrozole alone. Endometrial thickness was also measured in both study groups, and it was higher in participants taking Letrozole and Dexamethasone. Prior studies have similarly demonstrated efficacy for adjuvant Dexamethasone inducing ovulation and improving pregnancy rates in patients with PCOS-related subfertility. A comprehensive review of randomized controlled trials by (10) compared the effectiveness of glucocorticoid administration in the peri-implantation period in sub-fertile women undergoing assisted reproductive techniques. The results showed that live births following no glucocorticoid administration were 9% compared to 6%-21% with glucocorticoid administration. Similarly, clinical pregnancies following no glucocorticoids were 25% and 24% to 32% following glucocorticoids with therapy. Farzane et al. conducted a study to test the efficacy of Letrozole and Dexamethasone on ovulation and pregnancy rate in women with PCOS-related subfertility. They concluded that the mean diameter of follicles and endometrial thickness in both study groups (i.e., Letrozole only and Letrozole - Dexamethasone) were not statistically significant. However, the pregnancy rate in the Letrozole – Dexamethasone group was 23%, compared to 8% in the group taking only Letrozole. The results are encouraging as they showed a higher pregnancy rate from the combined usage of Letrozole and Dexamethasone. In a recent study done by Michael F. Neblett, Letrozole with Dexamethasone was given to Letrozole-resistant participants with PCOS-related subfertility (11). Their results showed that 79% ovulation was achieved by taking Letrozole and Dexamethasone, and 32% of the participants had live births. They evaluated 42 ovulation induction cycles by giving Letrozole on days 3 to 5 of the cycle, which was incrementally increased to 7.5 mg. Dominant follicles were observed after this dose, and Dexamethasone in the dose of 0.5 mg for 7 days was added when no dominance follicle was identified. The findings of our study align with and extend the growing body of evidence supporting the efficacy of Letrozole combined with Dexamethasone in improving ovulation outcomes and endometrial receptivity in women with PCOS-related subfertility. While prior studies, such as those by Farzane et al. and Michael F. Neblett, have highlighted the potential benefits of this combination therapy, our results present a stronger case for its superiority (8, 11). Specifically, the statistically significant improvements in both follicular diameter and endometrial thickness observed in our study underscore the enhanced efficacy of this regimen. Unlike Farzane et al., who found no significant difference in follicular diameter or endometrial thickness between the two treatment groups, our findings suggest that the synergistic effect of Dexamethasone with Letrozole not only facilitates follicular growth but also optimizes the endometrial environment for implantation (8). These differences may stem from variations in dosage protocols, population characteristics, or methodological rigor, underscoring the need for further research to standardize treatment guidelines. Moreover, while Neblett's study focused on Letrozole-resistant patients and demonstrated impressive ovulation and live birth rates with the combined therapy, our study also supports combined therapy for a demographically different population of women with PCOS-related subfertility (11). The improved follicular and endometrial outcomes observed in our study may translate into even higher pregnancy rates, as suggested by the positive correlation between these parameters and successful conception in previous research. The findings of our study suggest the treatment efficacy of Letrozole-Dexamethasone and its combined application for assisting women with subfertility. By demonstrating significant improvements across key clinical indicators, our findings provide compelling evidence for incorporating this regimen into routine clinical practice for managing PCOS-related subfertility. Future studies should build on these results to explore its application across diverse populations and its long-term implications for pregnancy and live birth rates.

Conclusion

This study highlights the superior efficacy of the Letrozole-Dexamethasone combination over Letrozole alone in managing PCOS-related subfertility, a significant issue faced by women suffering from this medical condition. The findings demonstrate substantial results in key

indicators such as follicular diameter and endometrial thickness, which are crucial for successful ovulation and implantation. These results align with the prior research, emphasizing the potential of Dexamethasone as an effective adjuvant in enhancing the outcomes of ovulation induction therapy. Our study also addressed some limitations observed in previous research, such as the non-significant differences in follicular and endometrial parameters reported by earlier researchers. The statistically significant improvements observed in this study underscore the synergistic effects of Letrozole and Dexamethasone, which enhance follicular development and optimize the uterine environment for implantation. By confirming and building upon existing evidence, this study provides a robust foundation for incorporating the Letrozole-Dexamethasone combination into routine clinical practice. The observed improvements in ovulatory and endometrial parameters suggest a promising role for this combination therapy in increasing pregnancy rates. Future research should explore its application across diverse populations, optimal dosage protocols, and long-term impacts on live birth rates. Ultimately, this study contributes to refining treatment strategies for PCOS-related subfertility, offering hope to women struggling with this condition.

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