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SAFETY, SIDE EFFECTS, AND PATIENT PROFILE IN LETROZOLE STEP-UP VS CONVENTIONAL PROTOCOLS FOR OVULATION INDUCTION IN UNEXPLAINED INFERTILITY

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Abstract

Objective: To evaluate and compare the safety profile, side effects, and patient demographics in women undergoing ovulation induction using letrozole step-up protocol versus conventional dosage protocol as part of intrauterine insemination (IUI) for unexplained infertility.

Introduction

Unexplained infertility affects 10–15% of couples, often diagnosed when standard fertility evaluations show normal results in both partners. Ovulation induction followed by IUI is a commonly recommended empirical treatment. Letrozole, an aromatase inhibitor, is increasingly used for this purpose due to its favorable effect profile compared to clomiphene citrate. Two popular regimens include a step-up approach (incremental dosing) and conventional fixed-dose administration. Comparative data regarding safety and tolerability between these protocols remain limited.

Materials and Methods

This randomized controlled trial was conducted in the Department of Obstetrics and Gynecology, Dr. Rajendra Prasad Government Medical College, Kangra, Himachal Pradesh, India (2021–2022). Sixty women with unexplained infertility were randomized into two groups:

Group A (Step-up): Letrozole began at 2.5mg on Day 2, increased daily by 2.5mg for four days.

Group B (Conventional): Letrozole 5mg daily from Day 2 to Day 6.

Patients were monitored for ovulatory response and side effects. Demographic/clinical characteristics, endocrine status, and adverse events were recorded and analyzed.

Results

Patient Profile

Age: Mean age was comparable; Group A: 28.66±3.89 years, Group B: 28.53±3.74 years.

Residence: Majority were rural (Group A: 96.67%, Group B: 93.33%).

Socioeconomic Distribution: Predominantly middle class.

Causes of Infertility: Primary infertility was slightly more common (Group A: 76.67%, Group B: 66.67%).

Endocrine and Semen Parameters

TSH, Prolactin, RBS: Both groups had mean values within normal reference ranges.

Semen Quality: Statistically significant difference in sperm concentration—a higher proportion in Group B had >50 million/ml, but sperm motility did not differ significantly.

Other Baseline Characteristics: Similar in both groups.

Safety and Side Effects

Abdominal Pain: Group A (Step-up) — 6 cases (20%), Group B (Conventional) — 7 cases (23.3%); not statistically significant (p=0.82).

Vaginal Bleeding: Slightly higher in Group A (5 cases vs 3), but not significant.

Ovarian Hyperstimulation Syndrome (OHSS): No cases reported in either group.

No serious adverse effects were noted in either group. There were no instances of multiple pregnancy, severe allergy, or systemic complications noted during the monitored cycles.

Cycle Cancellation and Tolerability

Cycle Cancellation Rate: Group A had a slightly lower cancellation rate (4.94%) compared to Group B (6.41%).

Treatment Completion: Majority of cycles were completed without discontinuation due to intolerance or complications.

Discussion

The findings indicate letrozole step-up and conventional protocols have similar safety and tolerability in women with unexplained infertility undergoing IUI. Abdominal pain and mild vaginal bleeding were the most common side effects, with no significant differences between groups. Importantly, neither protocol resulted in OHSS, a severe complication more common with gonadotropins. The favorable safety profile of letrozole compared to CC or gonadotropins is consistent with the published literature. Baseline characteristics related to age, endocrine profile, and socio-demographics were balanced, minimizing confounding.

The step-up protocol was associated with slightly better cycle viability and marginally lower cancellation rates, although differences in safety or major adverse events were negligible. These results are consistent with recent studies demonstrating low rates of serious side effects with letrozole-based ovulation induction.

The absence of multiple pregnancies or severe complications further supports the safety of oral letrozole regimens over more aggressive stimulation protocols commonly associated with higher-order multiples and OHSS.

Conclusion

Both letrozole step-up and conventional fixed-dose protocols are safe, well-tolerated, and appropriate for ovulation induction in women with unexplained infertility, with no significant difference in the frequency or severity of adverse events. Letrozole is a favorable choice for ovulation induction due to its minimal risk profile and ease of administration.

References

1. Katole A, Saoji AV. Prevalence of Primary Infertility and its Associated Risk Factors in Urban Population of Central India: A Community-Based Cross-Sectional Study. Indian J Community Med. 2019;44(4):337-341.
2. Mitwally MF, Casper RF. Letrozole for ovulation induction. Expert Rev Obstet Gynecol. 2006;1(1):15-27.
3. Kar S. Current evidence supporting “letrozole” for ovulation induction. J Hum Reprod Sci. 2013;6(2):93-8.
4. Homburg R. Clomiphene citrate—end of an era? A mini-review. Hum Reprod. 2005;20(8):2043-51.
5. Badawy A, Metwally M, Fawzy M. Randomized controlled trial of three doses of letrozole for ovulation induction in patients with unexplained infertility. Reprod Biomed Online. 2007;14(5):559-62.
6. Kaur J, Suri V, Gainder S, Arora A. Prospective randomized trial comparing efficacy of letrozole step-up protocol with letrozole plus gonadotropins for controlled ovarian stimulation and intrauterine insemination in patients with unexplained infertility. Arch Gynecol Obstet. 2019;300(6):1767-71.
7. Ali HA et al. Letrozole step-up versus fixed-dose protocols in ovulation induction in patients with unexplained infertility. Int J Chem Biochem Sci. 2024;25(14):100-108.
8. Zolton JR et al. Gonadotropins versus oral ovarian stimulation agents for unexplained infertility: a systematic review and meta-analysis. Fertil Steril. 2020;113(2):417-25.