Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/6sakww97

CLINICAL EFFICACY OF LETROZOLE STEP-UP PROTOCOL VERSUS CONVENTIONAL DOSAGE FOR OVULATION INDUCTION IN INTRAUTERINE INSEMINATION AMONG WOMEN WITH UNEXPLAINED INFERTILITY: A RANDOMIZED CONTROLLED TRIAL

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Abstract:
This study compares the efficacy of letrozole step-up protocol and conventional dosage for ovulation induction in intrauterine insemination (IUI) among women with unexplained infertility. Sixty participants were randomized into two groups: Group A received step-up letrozole dosing (starting 2.5 mg with daily increments) and Group B received a fixed dose of 5 mg daily. Outcomes included ovulation rates, follicular development, cycle cancellation, and pregnancy rates. Group A showed a slightly higher ovulation rate (95.06% vs. 93.59%) and total dominant follicles per cycle (77 vs. 74) with a lower cancellation rate (4.94% vs. 6.41%). Pregnancy rates were comparable initially (10% in both groups) but favored Group A in subsequent cycles (16.66% vs. 13.33%). Both protocols were effective, but the step-up regimen demonstrated sustainable cycle viability and follicular response benefits. These findings support the step-up protocol as a viable option in clinical practice.

Introduction:
Unexplained infertility affects 10-15% of infertile couples worldwide and presents a diagnostic challenge when standard evaluations yield no definitive cause. Intrauterine insemination (IUI) combined with ovulation induction remains a cornerstone empirical treatment to enhance pregnancy success in these cases. Letrozole, a third-generation aromatase inhibitor, has emerged as an effective alternative to clomiphene citrate by promoting ovulation with fewer anti-estrogenic side effects on the endometrium.
The conventional letrozole ovulation induction regimen involves a fixed dose of 2.5-5 mg daily for 5 days, but some patients demonstrate suboptimal responses. The step-up protocol, gradually increasing the dose over days, aims to optimize follicular recruitment and endometrial receptivity while

minimizing cycle cancellations and adverse effects. This randomized controlled trial compares these two letrozole protocols to evaluate efficacy and clinical outcomes in women undergoing IUI for unexplained infertility.

Materials and Methods:
The study enrolled 60 married women aged 18-40 years with unexplained infertility of at least 1 year duration, normal semen parameters, and patent fallopian tubes. Participants were randomized into Group A (step-up protocol: starting at 2.5 mg letrozole with daily increments of 2.5 mg over 4 days from menstrual day 2) and Group B (fixed dose: 5 mg letrozole daily from day 2 to 6).
Follicular growth and endometrial thickness were monitored by transvaginal ultrasound from day 11 onwards. When a dominant follicle ≥18 mm was observed, 10,000 IU human chorionic gonadotropin (hCG) was administered and IUI performed 36-40 hours later. Progesterone support was provided post-IUI. A maximum of 4 cycles were attempted. Outcomes assessed included ovulation rate, total dominant follicles, cycle cancellation rate, and pregnancy rate per cycle.

Results:
Both groups exhibited high ovulation rates: 95.06% in Group A and 93.59% in Group B. Group A had a higher number of total dominant follicles (77 cycles) compared to Group B (74 cycles), indicating enhanced follicular development with the step-up regimen.
Cancellation rates were lower in Group A (4.94%) than Group B (6.41%), suggesting better cycle viability. Pregnancy rates were equal (10%) in the first cycle but trended higher in Group A in subsequent cycles (16.66% vs. 13.33%).
No significant differences were observed in endometrial thickness or follicular size between groups. Mild side effects such as abdominal pain and vaginal bleeding were comparable, and no ovarian hyperstimulation syndrome cases occurred.

Discussion:
This study demonstrates that both the letrozole step-up and conventional fixed-dose protocols are effective for ovulation induction in IUI cycles among women with unexplained infertility. The step-up protocol showed modest but clinically relevant advantages including improved ovulation rates, more mature follicles, and fewer canceled cycles, which may contribute to improved cumulative pregnancy rates over multiple cycles.
The gradual increase in letrozole dose may better stimulate folliculogenesis without overstimulation risks, aligning with prior studies showing multi-follicular development with step-up regimens. Comparable endometrial thickness and tolerability between protocols indicate similar endometrial preparation and safety profiles.
Limitations include the moderate sample size and single-center design. Larger multicenter trials with longer follow-up are warranted to confirm these findings and optimize dosing strategies.

Conclusion:
Both letrozole step-up and conventional protocols effectively induce ovulation for IUI in unexplained infertility. The step-up protocol may provide advantages in follicular response, cycle viability, and pregnancy outcomes, supporting its use as a preferred ovulation induction strategy.

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