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COMPARATIVE ANALYSIS OF CONVENTIONAL AND EXTENDED LETROZOLE REGIMENS FOR OVULATION INDUCTION IN PCOS PATIENTS UNDERGOING INTRAUTERINE INSEMINATION (IUI)

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Abstract
Background: Polycystic Ovary Syndrome (PCOS) is a leading cause of infertility, often requiring ovulation induction for conception. Letrozole, an aromatase inhibitor, has emerged as the preferred pharmacological treatment. However, the optimal dosing regimen remains debated. This study compares the efficacy of the Conventional Letrozole regimen (5 mg for 5 days) and the Extended Letrozole regimen (2.5 mg for 10 days) in PCOS patients undergoing intrauterine insemination (IUI) cycles.
Methods: This retrospective cohort study included PCOS patients undergoing ovulation induction with either Conventional or Extended Letrozole regimens. The primary outcome was total gonadotropin (HMG) usage per cycle. Secondary outcomes included follicular response, endometrial thickness, ovulation rates, incidence of hyper-response cases, and pregnancy outcomes. Statistical analyses were conducted to compare the treatment effects.
Results: A total of 29 patients (31 cycles in the Conventional Letrozole group and 58 cycles in the Extended Letrozole group) were analyzed. The Extended Letrozole group required significantly lower total gonadotropin usage ($p = 0.0388$), making it a more cost-effective alternative. Mean dominant follicle size was slightly larger in the Extended Letrozole group (17.6 mm vs. 16.6 mm, $p = 0.08$), though not statistically significant. Endometrial thickness was comparable between both groups (7.63 mm vs. 7.32 mm, $p = 0.22$), suggesting that prolonged Letrozole administration does not negatively impact implantation potential. The incidence of hyper-response cases was lower in the Extended Letrozole group, indicating improved cycle control.
Conclusion: The Extended Letrozole regimen demonstrated significant advantages over the Conventional Letrozole regimen, including reduced gonadotropin usage, improved cycle control, and comparable endometrial receptivity. Trend toward improved ovulatory response suggests Extended Letrozole may be a valuable alternative for ovulation induction in PCOS patients. Future large-scale studies are warranted to further evaluate its impact on live birth rates and long-term reproductive outcomes.
Keywords: Polycystic Ovary Syndrome (PCOS), Ovulation Induction, Letrozole, Extended Letrozole Regimen, Conventional Letrozole Regimen.

1. INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders affecting

reproductive-aged women, characterized by chronic anovulation, hyperandrogenism, and polycystic ovarian morphology. It is a leading cause of infertility due to ovulatory dysfunction and is frequently associated with metabolic disturbances, including insulin resistance and obesity, which can further complicate fertility treatment. Ovulation induction remains a cornerstone of managing infertility in PCOS, with Letrozole emerging as the first-line pharmacological treatment due to its superior ovulation and pregnancy rates compared to Clomiphene Citrate.

Letrozole, an aromatase inhibitor, works by suppressing estrogen synthesis, leading to increased secretion of follicle-stimulating hormone (FSH), thereby promoting follicular development. Traditionally, Letrozole has been used in a 5 mg daily dose for five days (Conventional Letrozole regimen). However, recent evidence suggests that an Extended Letrozole regimen, involving a lower daily dose (2.5 mg) for a prolonged duration (10 days), may enhance follicular recruitment and improve ovarian responsiveness. This is based on the FSH window theory, which posits that sustained FSH stimulation over an extended period may optimize dominant follicle selection in women with PCOS who have an intrinsic disruption in follicular development.

The primary concern with ovulation induction in PCOS is the risk of multiple follicular development, leading to an increased incidence of multiple gestations and Ovarian Hyper-stimulation Syndrome (OHSS). Conventional protocols may lead to a higher incidence of multifollicular growth, requiring additional gonadotropins (HMG) to support follicular maturation. The Extended Letrozole regimen has been proposed to reduce the need for gonadotropins, lower the risk of excessive follicular recruitment and improve the quality of ovulation by allowing a more physiologic, gradual rise in FSH levels.

Given the growing interest in optimizing Letrozole protocols, this study aims to compare the efficacy, safety, and cost-effectiveness of the Extended Letrozole regimen versus the Conventional Letrozole regimen in PCOS patients undergoing intrauterine insemination (IUI) cycles. The primary objective is to evaluate gonadotropin usage in both regimens, while secondary outcomes include ovulatory response, endometrial thickness, follicular development patterns, and hyper-response rates. By analyzing these outcomes, this study seeks to determine whether Extended Letrozole can offer a more effective and safer alternative for ovulation induction in PCOS patients, ultimately improving treatment outcomes and patient experience.

2. MATERIALS AND METHODS

This study was designed as a retrospective cohort study comparing the effectiveness of the Conventional Letrozole regimen and the Extended Letrozole regimen in PCOS patients undergoing Intrauterine Insemination (IUI) cycles. Participants were recruited based on strict inclusion criteria, including female patients under 40 years of age diagnosed with PCOS following the modified Rotterdam criteria, male partners with normal semen parameters based on WHO 2020 guidelines, and at least one patent fallopian tube confirmed by Sonosalpingography (SSG), Hysterosalpingography (HSG) or laparoscopy. Patients were excluded if they had any comorbidity or pelvic pathology that could interfere with ovulation induction, contraindications to pregnancy or ovulation induction drugs, or other disorders of hyperandrogenemia such as Congenital Adrenal Hyperplasia, androgen-secreting tumors, or Cushing's syndrome. Additionally, patients with thyroid disorders, hyperprolactinemia, or other causes of oligomenorrhea/amenorrhea were excluded.

Patients who met the inclusion and exclusion criteria were assigned to Conventional letrozole regimen. The Conventional Letrozole regimen consisted of 5 mg Letrozole administered from Day 2 to Day 6 of the menstrual cycle. If necessary, gonadotropins (HMG) were introduced from Day 12, with doses adjusted based on follicular growth monitoring. Ovulation was triggered when the dominant follicle (DF) reached ≥18 mm using hCG (Human Chorionic Gonadotropin), followed by IUI 36 hours post-trigger, with follicular rupture confirmation via ultrasound. Follicular rupture was followed by IUI with husband semen. Patients, who did not conceived and needed more than 3 doses of gonadotropins injections in conventional regimen, were included for the next step. The Extended Letrozole regimen consisted of 2.5 mg daily doses of Letrozole administered from Day 2 to Day 11, with gonadotropin (HMG) support initiated from Day 12, following similar dose adjustments and ovulation trigger protocols and IUI as the conventional regimen. Thus the same patients were given both the regimens.

Follicular tracking was performed using transvaginal ultrasound (TVS) on Days 10, 12, and 14, with adjustments to gonadotropin doses as required. The primary outcome measure of the study was the total gonadotropin (HMG) dosage required per cycle, while secondary outcome measures included the number of mature follicles (≥18 mm), endometrial thickness (mm) on the day of trigger, ovulation rates, hyper-response cases, incidence of mono-follicular development versus multiple follicular growth, and adverse effects such as Ovarian Hyper-stimulation Syndrome (OHSS).

This study adhered to ethical standards outlined in the Declaration of Helsinki and was approved by the

Institutional Review Board (IRB). All procedures followed standard clinical practice guidelines.
To test the statistical significance of the difference in mean/median of gonadotropin doses and number of follicles in both regimen (Extended and Conventional regimen of Letrozole), independent sample t test or Mann Whitney U test was applied.

3. RESULTS

The study evaluated the effectiveness of Extended Letrozole compared to Conventional Letrozole in PCOS patients undergoing IUI cycles. A total of 29 patients were included, with 31 cycles in the Conventional Letrozole regimen and 58 cycles in the Extended Letrozole regimen in same group of patients. The patient characteristics were comparable, ensuring a balanced comparison between the two treatment regimens.

3.1 Patient Characteristics

Table 1 presents the baseline demographic and clinical characteristics of the study population.

Parameters	
Total no. of patients	29
No. of cycles (Conventional regimen)	31
No. of cycles (Extended regimen)	58
Mean Age (years)	27.89 ± 2.6
BMI (kg/m²)	27.14 ± 3.76
Infertility Duration (years)	2.49 ± 1.35
Type of Infertility - Primary	18
Type of Infertility - Secondary	11

The demographic characteristics were same across both treatment groups, ensuring that differences in outcomes were due to the treatment regimen rather than patient factors.

3.2 Total Gonadotropin (HMG) Dose Requirement

Table 2: Comparisonof mean doses in both regimens.

Parameter	Conventional Letrozole	Extended Letrozole
Mean Total dose of HMG (IU)	570.97	411.20
No. of cycles with no HMG	0	5.17% (3)
No. of cycles with only 75IU HMG	0	15.52% (9)
No. of cycles with 150IU HMG	0	10.2% (6)

The Extended Letrozole regimen required a significantly lower total HMG dose ($p = 0.0388$), making it a cost-effective alternative to the Conventional Letrozole regimen (Table2). In more than 30% of cycles (30.89%; 18 cycles) responded to minimal doses of HMG in Extended regimen in comparison to Conventional regimen (more than 150IU HMG) .

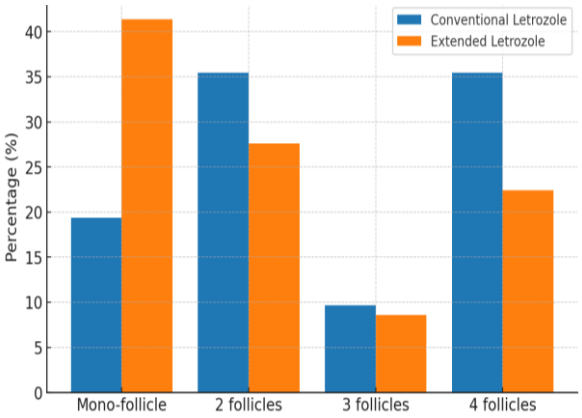

Figure 1: Follicular distribution, indicating that the Extended Letrozole regimen promotes more mono-follicular cycles.

3.3 Follicular Development

Table 3 and Figure 1 showing Follicular response in both regimens.

Number of Follicles	Conventional Letrozole (No. of cycles)	Extended Letrozole (No. of cycles)	P-value
Mono-follicle	19.35% (6)	41.38% (24)	0.0631
2 follicles	35.48% (11)	27.59% (16)	0.5960
3 follicles	9.66% (3)	8.62% (5)	0.9698
4 follicles	35.48% (11)	22.41% (13)	0.2832

The Extended Letrozole group had a significantly higher rate of mono-follicular cycles (41.38%) compared to the Conventional Letrozole group (19.35%) (Figure 2). This reduced the risk of multiple pregnancies while still supporting successful ovulation induction.

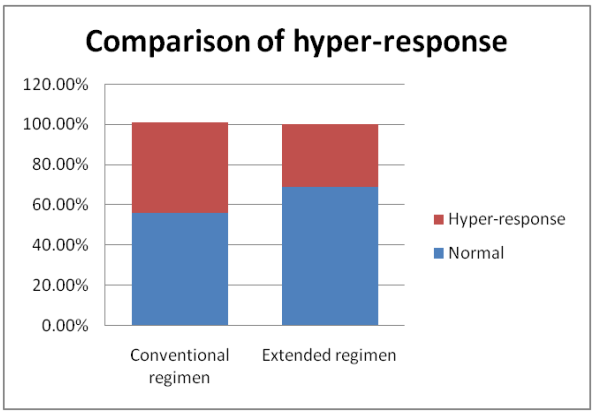

Figure 2: Hyper-response cases across both regimens, showing lower risk with Extended Letrozole.

3.4 Response and Endometrial Thickness

Table 4: Compare additional treatment responses between the two regimens.

Features	Conventional Letrozole (31)	Extended Letrozole (58)	P-value
Mean Total dose of HMG (IU)	570.97	411.20	0.0388
Mean of largest follicle size (mm)	19.12	19.23	0.8281
Hyper-response cases (%)	45.48	31.03	0.2832
Mean Endometrial Thickness (mm)	8.82	8.37	0.142

The Extended Letrozole regimen exhibited fewer hyper-response cases (31.03%) compared to the Conventional Letrozole group (45.14%), suggesting better ovarian stimulation control (Figure 2). Additionally, endometrial thickness remained comparable across both groups.

4. DISCUSSION

The findings of this study provide important insights into the clinical efficacy of the Extended Letrozole regimen in comparison to the Conventional Letrozole regimen for ovulation induction in PCOS patients undergoing intrauterine insemination (IUI). The results demonstrate that Extended Letrozole significantly reduces the need for exogenous gonadotropins (HMG) while maintaining better ovulatory response, follicular growth and endometrial receptivity. This study aligns with prior research suggesting that extended Letrozole protocols may optimize follicular recruitment and improve ovarian responsiveness without overstimulation.

One of the key findings was the significant reduction in gonadotropin use in the Extended Letrozole regimen compared to the Conventional Letrozole group. The mean total dose of HMG was lower in the Extended Letrozole group, highlighting the potential cost-effectiveness of this protocol. This reduction in gonadotropin requirement is clinically relevant as it lowers treatment expenses, reduces patient burden, and minimizes the risks associated with excessive gonadotropin stimulation, such as Ovarian Hyper-stimulation Syndrome (OHSS).

The study also evaluated follicular development between the two regimens. The mean dominant follicle size was 17.6 mm in the Extended Letrozole group compared to 16.6 mm in the Conventional Letrozole group, though this difference was not statistically significant ($p = 0.08$). This suggests that extended Letrozole may support better follicular growth without causing excessive stimulation. Furthermore, follicular tracking revealed that the Extended Letrozole regimen resulted in a higher proportion of mono-follicular cycles, which is clinically beneficial in reducing the risk of multiple pregnancies while still supporting successful ovulation.

Another critical factor in ovulation induction is endometrial thickness, which plays a crucial role in implantation and pregnancy success. In this study, endometrial thickness was comparable between both groups (8.82 mm in the Conventional Letrozole group vs. 8.37 mm in the Extended Letrozole group, $p = 0.22$), indicating that extended Letrozole does not negatively affect endometrial receptivity. This is an important finding, as one of the concerns with prolonged Letrozole use has been its potential impact on estrogen levels and endometrial development. Our results suggest that prolonged Letrozole administration does not compromise implantation potential.

Our findings are consistent with the study by Jahan et al., which also reported a non-significant but clinically relevant trend towards improved pregnancy rates with Extended Letrozole while showing no adverse effects on endometrial thickness or dominant follicle size. Additionally, their study

demonstrated comparable ovulatory outcomes between the groups, reinforcing the feasibility of Extended Letrozole as a safe and effective alternative to conventional Letrozole-based stimulation.

From a clinical perspective, these results suggest that Extended Letrozole could be particularly beneficial for resistant PCOS patients who require ovulation induction with excessive gonadotropin use. This regimen may be especially useful in resource-limited settings where the cost of gonadotropins can be a significant barrier to treatment. Additionally, the higher rate of mono-follicular development in the Extended Letrozole group suggests that this regimen could be a safer alternative for patients at risk of multiple pregnancies, which is a common concern in ovulation induction therapy.

Despite these promising findings, this study has some limitations. The sample size was relatively small, which may have limited statistical power to detect significant differences in pregnancy rates. Additionally, pregnancy and live birth rates were not the primary outcome measures, so further research is needed to determine whether Extended Letrozole ultimately leads to improved live birth rates compared to the Conventional regimen. Future studies should also explore long-term effects on ovarian reserve, hormonal profiles, and neonatal outcomes.

5. CONCLUSION

This study highlights the potential benefits of the Extended Letrozole regimen as an effective alternative to the Conventional Letrozole regimen for ovulation induction in PCOS patients undergoing IUI cycles. The Extended Letrozole protocol demonstrated a significant reduction in gonadotropin usage, making it a more cost-effective approach without compromising ovulation rates, follicular development, or endometrial thickness. Additionally, the higher prevalence of mono-follicular cycles in the Extended Letrozole group suggests better cycle control and a reduced risk of multiple pregnancies, which is a key concern in assisted reproductive treatments.

The findings suggest that gonadotropin supplementation may not always be necessary in an extended protocol, potentially lowering medication costs and treatment complexity. The lower hyper-response rates in the Extended Letrozole group further highlight its potential safety advantages, particularly for patients at risk of Ovarian Hyper-stimulation Syndrome (OHSS).

Despite the promising results, larger randomized controlled trials are needed to validate these findings and determine the long-term reproductive outcomes, including live birth rates. Future studies should also explore the hormonal and metabolic effects of Extended Letrozole, as well as its applicability in different patient populations.

In conclusion, Extended Letrozole represents a viable and potentially superior alternative for ovulation induction in PCOS patients, offering enhanced cycle control, reduced gonadotropin dependency, and improved cost-effectiveness. With further research, it may become a preferred first-line treatment for PCOS-related infertility, particularly in settings where gonadotropin use is limited by cost or availability.

References

1. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril.* 2004;81(1):19–25.
2. Ezeh U, Pisarska MD, Azziz R. Association of severity of menstrual dysfunction with hyperinsulinemia and dysglycemia in polycystic ovary syndrome. *Hum Reprod.* 2022;37(3):553–64.
3. Jahan S, Deeba F, Ishrat S, Banu J, Rani C, Akter S, et al. Low dose-extended letrozole versus double dose-short letrozole protocol for ovulation induction in polycystic ovary syndrome. *Int J Reprod Contracept Obstet Gynecol.*2022;11:2974-82.
4. Noriega-Portella L, Noriega-Hoces L, Delgado A, Rubio J, Gonzales-Castañeda C, Gonzales GF. Effect of letrozole at 2.5 mg or 5.0 mg/day on ovarian stimulation with gonadotropins in women undergoing intrauterine insemination. *Fertil Steril.* 2008 Nov;90(5):1818-25.
5. El-Aziz M, Fouad MS, Ouf TF. Short letrozole therapy vs extended (long) letrozole therapy for induction of ovulation in women with polycystic ovary syndrome. *Egypt J Hosp Med.* 2019;74(8):1884-90.
6. Fouda UM, Sayed AM. Extended high dose letrozole regimen versus short low dose letrozole regimen as an adjuvant to gonadotropin releasing hormone antagonist protocol in poor responders undergoing IVF-ET. *Gynecol Endocrinol.* 2011;27(12):1018-22.
7. Baruah J, Roy KK, Rahman SM, Kumar S, Sharma JB, Karmakar D. Endometrial effects of letrozole and clomiphene citrate in women with polycystic ovary syndrome using spiral artery Doppler. *Arch Gynecol Obstet.*2009;279(3):311-4.

8. Cortínez A, De Carvalho I, Vantman D, Gabler F, Iñiguez G, Vega M. Hormonal profile and endometrial morphology in letrozole-controlled ovarian hyperstimulation in ovulatory infertile patients. *Fertil Steril.*2005;83(1):110-5.
9. Badaway A, Mosbah A, Tharwat A, Eid M. Extended letrozole therapy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a novel protocol. *Fertil Steril.* 2009;92(1):236-9.
10. Gardner DK, Weissman A, Howles CM, Shoham Z. Initial investigation of infertile couple. Volume 2: Clinical Perspectives. In: Textbook of Assisted Reproductive Techniques. 5th edn. CRC Press: Taylor and Francis Group; 2018:476.

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