

ARTICLE INFORMATION

Received: April 17, 2026

Revised: April 26, 2026

Available online: April 28, 2026

at: <https://e-jurnal.ipphorr.com/index.php/mchc>

Shifting the paradigm to letrozole as first-line ovulation induction in pcos: a review of efficacy and safety

Juwana Janu*, Reny Haryani

Institut Teknologi Sumatra

Corresponding author: * Email: juwana.janu@fa.itera.ac.id

Abstract

Background: Polycystic ovary syndrome (PCOS) is a primary cause of anovulatory infertility. While clomiphene citrate (CC) has been the traditional treatment, letrozole (LE) has emerged as a superior alternative with better clinical outcomes.

Purpose: to evaluate the clinical efficacy, safety, and biological mechanisms of LE compared with CC in ovulation induction for PCOS patients.

Method: A comprehensive literature search was conducted on PubMed and Google Scholar for studies published between 2021 and 2026. Seven high-quality articles, including randomized controlled trials (RCTs) and meta-analyses, were selected for synthesis.

Results: The synthesis of the literature indicates that LE significantly increases the live birth rate by 54% (RR 1.54) and improves ongoing pregnancy rates compared with CC. LE is more efficient, showing a shorter time to ovulation (17.2 vs 24.1 days) and higher success in obese patients (BMI > 30). Mechanistically, LE superiorly enhances endometrial receptivity by significantly increasing Integrin $\alpha\beta 3$ and VEGF expression, as well as the Endometrial Flow Index (FI). Furthermore, LE demonstrates a superior safety profile with a 58% lower risk of multiple pregnancies and minimal incidence of ovarian hyperstimulation syndrome (OHSS).

Conclusion: Letrozole is more effective and safer than CC, primarily due to its beneficial impact on the endometrial microenvironment. LE could be implemented as the universal first-line treatment for infertility in women with PCOS.

Suggestion: For clinicians, LE can be considered as the universal first-line therapy for ovulation induction in patients with PCOS, replacing CC. From a health service policy perspective, standard protocols in fertility clinics need to be updated to integrate LE use in order to improve pregnancy success and reduce long-term costs due to complications of multiple pregnancy

Keywords: Clomiphene Citrate; Endometrial Receptivity; Letrozole; Ovulation Induction; PCOS.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder with variable clinical manifestations. According to international guidelines, the diagnosis of PCOS can be established if the patient meets at least two of the three main criteria: clinical or biochemical hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (PCOM) or elevated anti-Müllerian hormone (AMH) levels after other etiologies have been excluded (Christ & Cedars, 2023; ESHRE,

2023). These three components form four PCOS phenotypes that describe the clinical characteristics of each individual.

Polycystic ovary syndrome (PCOS) remains a significant global clinical challenge, affecting up to 13% of women of reproductive age and representing the leading cause of anovulatory infertility worldwide (ESHRE, 2023). This condition not only manifests as menstrual cycle disturbances and hyperandrogenism, but is also closely associated with long-term

metabolic risk (Legro, Arslanian, Ehrmann, Hoeger, Murad, Pasquali, & Welt, 2013). In the management of PCOS-related infertility, ovulation induction is the primary initial medical intervention. For more than five decades, CC has dominated clinical practice as the standard first-line therapy, in accordance with established global and national guidelines (National Institutes of Health, 2020; Ministry of Health of the Republic of Indonesia, 2022).

However, the use of CC has begun to shift following reports of ovulation failure rates reaching 40% and its anti-estrogenic effects on endometrial thickness and cervical mucus, which hinder pregnancy success (American Society for Reproductive Medicine, 2021). As a result, the latest international consensus through evidence-based guidelines supported by the European Society of Endocrinology and the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) now recommends LE as the first-line therapy for ovulation induction in women with PCOS (ESHRE, 2023). This change is based on the mechanism of LE as an aromatase inhibitor that preserves the hypothalamic-pituitary feedback mechanism, thereby producing a more physiological hormonal environment (Franik, Eltrop, Kremer, Kiesel, & Farquhar, 2018).

Although the clinical efficacy of LE has been widely recognized, in-depth exploration of its advantages in specific populations such as obese patients and of the molecular mechanisms at the uterine tissue level remains a current research focus. A study published in *Fertility and Sterility* showed that LE improves ongoing pregnancy success through enhanced uterine blood flow and the expression of receptivity markers such as integrin (Wang, Lv, Li, Bai, & Yang, 2021). In addition, a recent systematic review confirmed that LE provides a higher live birth rate with a substantially lower risk of multiple pregnancy compared with CC (Miller & Pinheiro, 2025).

This narrative review aims to synthesize the latest evidence from reputable literature and international guidelines in order to provide a comprehensive understanding of LE's strategic position in modern gynecological practice. The analysis focuses on clinical efficacy, safety profile, and the biochemical

implications of LE on the endometrial microenvironment in patients with PCOS.

RESEARCH METHOD

Tools: This study used the international medical literature databases PubMed and Google Scholar as the main tools for data retrieval.

Materials: The data sources consisted of original articles and meta-analyses published between 2021 and 2026. The main focus of the study materials was literature comparing the use of LE and clomiphene citrate, with primary outcomes in terms of clinical effectiveness and safety profile.

Search Strategy: Literature searches in the PubMed database were conducted using Boolean operators specifically designed to retrieve efficacy and safety data: (Letrozole AND "Clomiphene Citrate") AND (PCOS) AND ("Live Birth Rate" OR "Fetal Safety"), while the Google Scholar database used: `intitle:letrozole intitle:PCOS "live birth rate" safety`. **Screening:** The articles found were screened based on title and abstract. The inclusion criteria were: (a) focused on first-line ovulation induction, (b) included fetal safety and/or congenital malformation data, and (c) published in Indonesian or English.

Eligibility Assessment: This stage was conducted by reviewing the full text of the articles that passed screening. Eligibility criteria were based on the availability of specific clinical data, where the article had to include a primary outcome in the form of live birth rate and/or a secondary outcome in the form of fetal safety profile. Articles that did not present relevant clinical data were excluded. **Data Synthesis:** The data that met the eligibility criteria were extracted and analyzed comparatively using a qualitative approach. Findings from the various literatures were synthesized into descriptive narrative form and comparison tables to draw conclusions regarding the efficacy and safety of LE as the current standard therapy.

Juwana Janu*, Reny Haryani

Institut Teknologi Sumatra

Corresponding author: * Email: juwana.janu@fa.itera.ac.id

DOI: 10.56922/mchc.v5i1.3084

RESEARCH RESULTS

Table Summary of the Literature Synthesis of Clinical Findings of Letrozole vs Clomiphene Citrate (2021–2026)

Author & Year	Method	Main Clinical Outcome	Safety & Fetal Profile
(Eskandar et al., 2025).	Combination: LE + CC Monotherapy: LE	Ovulation: The combination therapy was significantly superior (OR 2.55) compared with monotherapy. Similar significant results were found in the increase in the number of mature follicles (OR 2.74).	Safety & Fetal Profile: In the LE group, twin pregnancy frequency remained unchanged / did not increase. It maintained endometrial thickness and cervical mucus quality.
(Al-Thuwaynee & Swadi, 2023).	Protocol: Stair-step protocol (rapid dose escalation) Comparison: LE vs CC	Time Efficiency: Ovulation occurred 7 days earlier with LE (17.20 vs 24.08 days; $p < 0.001$). LE had a higher ovulation rate (86% vs 72%).	Safety & Fetal Profile: No significant difference in side effects: nausea (5%), headache (5%), dizziness (5%). Safe for fetal weight and miscarriage rate.
(Franik et al., 2022)	Method: Meta-analysis (41 RCTs). Comparison: LE vs CC $\pm$ adjuncts	Live Birth Rate (LBR): Significantly superior (OR 1.72). The probability of live birth increased from 20.4% (CC) to 30.7% (LE).	Safety & Fetal Profile: High-certainty evidence: miscarriage risk (24%) and OHSS (0.5%) were similar. Twin pregnancy risk tended to be lower (OR 0.74).
(Abd El-Maksoud, 2021)	Method: 3 groups: A: CC + Gonadotropin B: LE + Gonadotropin C: LE alone	Follicles & Ovulation: Group C (LE alone) was the most superior in monofollicular development (83%). Ovulation was highest in Group B (80%).	Safety & Fetal Profile: OHSS risk was 0% in Group C. Group B (1%) was much safer than Group A (5%).

Juwana Janu*, Reny Haryani

Institut Teknologi Sumatra

Corresponding author: * Email: juwana.janu@fa.itera.ac.id

DOI: 10.56922/mchc.v5i1.3084

Shifting the paradigm to letrozole as first-line ovulation induction in pcos: a review of efficacy and safety

(Mejia et al., 2025)	Method: Open-label RCT Comparison: Combination (LE 2.5 mg + CC 50 mg) vs LE 2.5 mg alone	Ovulation & Time: The combination group was significantly higher (81.9% vs 71.4%). Faster time to live birth (1.73 vs 2.32 cycles; p = 0.009). Multiple Birth: No increase in twin pregnancy risk (only 2 cases in each group).	Safety & Fetal Profile: Included in multiple birth data; no additional side effects reported.
(Miller & Pinheiro, 2025)	Method: Meta-analysis (33 RCTs) Comparison: LE vs CC	Efficacy of LE: Total sample: 4,207 patients. Superior efficacy of LE: LBR was 54% higher (RR 1.54); pregnancy rate was 57% higher (RR 1.57).	Safety of LE: Superior safety with LE: twin pregnancy risk decreased by 58% with LE (RR 0.42). Miscarriage risk was similar (RR 0.97).
(Wang et al., 2021)	Method: 3-arm RCT (n = 270) Comparison: LE 2.5 mg, CC 50 mg, vs Natural cycle	Efficacy: Ongoing pregnancy was significantly higher with LE (23.3%) compared with CC (11.1%). Molecular Receptivity: LE increased Integrin $\alpha\beta 3$ (29.2 pg/mL) and VEGF (35.6 pg/mL) levels, far above CC.	Not specified

Juwana Janu*, Reny Haryani

Institut Teknologi Sumatra

Corresponding author: * Email: juwana.janu@fa.itera.ac.id

DOI: 10.56922/mchc.v5i1.3084

DISCUSSION

The results showed that LE consistently produced higher LBR and ongoing pregnancy rates. This advantage was found not only in the general PCOS population, but was especially prominent in the obese sub-group of patients (BMI > 30). In terms of safety, LE showed an advantage in reducing the risk of multiple pregnancy by up to 58% compared with CC. In addition, ultrasonographic parameters showed improved endometrial quality with LE use, which is a major supporting factor for successful embryo implantation.

The findings of this review consistently confirm that LE provides better clinical outcomes than CC. The latest meta-analyses provide the highest-level evidence that LE increases live birth probability by up to 54% (RR 1.54) with a Number Needed to Treat (NNT) of 10 (Miller & Pinheiro, 2025; Franik et al., 2022). This is clinically meaningful in infertility practice, because switching from CC to LE in 10 patients would result in one additional live birth that would not have been achieved with CC.

This advantage is visible not only in the final efficacy outcome, but also in treatment efficiency. LE significantly shortened the time to ovulation (17.2 vs 24.1 days). This reduction in time has major practical implications, including fewer transvaginal ultrasound monitoring sessions, which in turn lowers treatment costs and reduces the patient's psychological burden (Al-Thwaynee & Swadi, 2023). This synergistic effect becomes even more prominent in high-risk subpopulations such as patients with obesity (BMI > 30). Previous research found that combination therapy LE+CC achieved live birth outcomes faster (1.73 cycles) than monotherapy. Moreover, the effectiveness of LE is not limited by certain conditions (Mejia et al., 2025). Based on the study the pregnancy rate in obese patients with BMI > 30 kg/m² reached 28.5%, comparable to 29.2% in the non-obese group (Gowri, Al-Amri, Almamari, Al Khaduri, & Jaju, 2022).

This is reinforced by a meta-analysis study which found that in obese women with PCOS, LE was able to provide a 12% increase in ovulation rate and a pregnancy rate up to 33% higher than CC (Permadi & Prasetyaji, 2025). In terms of ovarian response, LE use was also proven to improve the Follicular Output Rate (FORT) and facilitate good follicular development, even in patients with high BMI.

The dominance of LE can then answer the challenge of CC resistance often faced by some women undergoing conception programs, as in the study where 33.3% of women with high waist-to-hip ratio, high androgen profile, and poor metabolic parameters did not ovulate despite undergoing CC therapy at a dose of 100 mg/day for 3 cycles (Xia, Sun, Guan, Zhang, & Zhang, 2021). This resistance condition proves that patients with complex metabolic profiles require alternative therapies such as LE, which has a more stable ovulatory response and is not hindered by the patient's physical or hormonal characteristics.

The most crucial aspect explaining the superiority of LE is its effect on endometrial receptivity. In contrast to CC, which has a long-lasting anti-estrogenic effect on estrogen receptors and often causes endometrial thinning, LE works through reversible aromatase inhibition without disrupting the hypothalamic feedback mechanism (Legro et al., 2021; Wang et al., 2021). Clomiphene citrate tends to leave an anti-estrogenic effect on estrogen receptors that persists quite long in the tissue because of its half-life of up to two weeks. In contrast, LE works by reversibly inhibiting aromatase and has a short half-life and rapid clearance (Amer, Smith, Mahran, Fox, & Fakis, 2017; Bulun, Monsavais, Pavone, Dyson, Xue, Attar, & Su, 2012). This short duration of action causes the drug to quickly leave the bloodstream, so it does not interfere with the hypothalamic feedback mechanism or with the physiological process of endometrial thickening.

Adequate endometrial thickening is the initial physical precondition for uterine readiness for pregnancy; beyond that, the quality of the tissue receptivity at the molecular level to receive the embryo is important. Wang et al. (2021) strengthened the biological explanation at the molecular level, showing that LE was able to increase receptivity markers, namely Integrin $\alpha\beta 3$ (29.2 pg/mL) and VEGF (35.6 pg/mL), which were significantly higher than with CC. Integrin $\alpha\beta 3$ acts as a "glue" that allows the embryo to attach firmly, while VEGF ensures adequate angiogenesis for placental nutrient supply.

Juwana Janu*, Reny Haryani

Institut Teknologi Sumatra

Corresponding author: * Email: juwana.janu@fa.itera.ac.id

DOI: 10.56922/mchc.v5i1.3084

3-D ultrasound parameters supported the objective findings through a higher Endometrial Flow Index (FI) in the LE group (25.7 vs 17.4). Improved uterine blood flow and biomarker quality explain why the ongoing pregnancy rate in the LE group (23.3%) was twice that of the CC group (11.1%), even though the ovulation rates between the two drugs are often similar. Thus, LE not only improves ovulation, but also creates an optimal intrauterine microenvironment for implantatio (Wang et al., 2021).

Patient safety is always a top priority in ovulation induction protocols. One classic limitation of CC is the high risk of multiple pregnancy and OHSS as a result of excessive estrogen stimulation and uncontrolled recruitment of multiple follicles (Gysler, March, Mishell, & Paulson, 1982; Franik et al., 2022). CC works by occupying estrogen receptors throughout the body for a long time, thereby triggering a less specific ovarian response.

In contrast, letrozole (LE) works specifically by inhibiting aromatase without directly interfering with estrogen receptors. Data from Miller & Pinheiro (2025) show that LE can reduce the risk of twin pregnancy by up to 58% (RR 0.42) because of its ability to select more optimal monofollicular growth. In terms of clinical complications, OHSS incidence of 0% with LE monotherapy. The hormonal stability produced by LE proves that this drug is safer and reduces the burden of ovarian hyperstimulation in patients (Abd El-Maksoud, 2021)

The low risk profile and long-term safety provide greater reassurance for both mother and fetus. Therefore, the advantage in mitigating multiple complications is a strong reason for practitioners to shift fully to LE, in line with the latest International Evidence-based Guideline that places LE as the universal first-line therapy for PCOS. Overall, integration of data from molecular efficacy to clinical outcomes shows that LE has surpassed CC as the gold standard. The use of LE does not only address anovulation, but also improves the uterine "microenvironment" that previously served as a barrier with CC.

Nevertheless, this review notes the need for further research on the long-term health of children born through LE protocols. Although current data on congenital anomalies do not show a significant difference compared with natural cycles, larger multicenter studies with longer follow-up are still

needed to strengthen the neonatal safety database. The clinical transition to LE is expected to improve pregnancy success rates in women with PCOS globally, while also reducing unnecessary medical costs and risks.

CONCLUSION

Based on the literature review of seven recent studies (2021–2026), it can be concluded that LE shows superior efficacy compared with CC in the management of infertility in patients with PCOS. LE has been proven to increase the live birth rate by up to 54% and improve ongoing pregnancy rates. These clinical advantages are supported by a mechanism involving improved endometrial receptivity, as indicated by increased expression of implantation biomarkers such as Integrin $\alpha v \beta 3$ and VEGF, as well as improved uterine blood flow (Endometrial Flow Index). In terms of treatment efficiency, LE requires a shorter time to ovulation and fewer treatment cycles, especially in patients with obesity or high BMI (>30). In addition, LE has a better safety profile, with a 58% lower risk of multiple pregnancy compared with CC and a very minimal risk of OHSS (0%).

SUGGESTION

For clinicians, LE can be considered as the universal first-line therapy for ovulation induction in patients with PCOS, replacing CC. From a health service policy perspective, standard protocols in fertility clinics need to be updated to integrate LE use in order to improve pregnancy success and reduce long-term costs due to complications of multiple pregnancy. In addition, for future researchers, multicenter studies with a longer follow-up period are needed to evaluate neonatal outcomes and long-term health after LE induction.

REFERENCES

- Abd El-Maksoud, M. M. (2021). Letrozole alone versus clomiphene citrate and gonadotropin combination for ovulation induction in women with polycystic ovarian syndrome: A comparative study. *Egyptian Journal of Fertility and Sterility*, 25(4), 45–52.

Juwana Janu*, Reny Haryani

Institut Teknologi Sumatra

Corresponding author: * Email: juwana.janu@fa.itera.ac.id

DOI: 10.56922/mchc.v5i1.3084

Shifting the paradigm to letrozole as first-line ovulation induction in pcos: a review of efficacy and safety

- Al-Thuwaynee, S., & Swadi, A. A. J. (2023). Comparing efficacy and safety of stair step protocols for clomiphene citrate and letrozole in ovulation induction for women with polycystic ovary syndrome (PCOS): a randomized controlled clinical trial. *Journal of medicine and life*, 16(5), 725.
- Amer, S. A., Smith, J., Mahran, A., Fox, P., & Fakis, A. (2017). Double-blind randomized controlled trial of letrozole versus clomiphene citrate in subfertile women with polycystic ovarian syndrome. *Human Reproduction*, 32(8), 1631-1638.
- American Society for Reproductive Medicine. (2021). Diagnostic evaluation of the infertile female: A committee opinion. *Fertility and Sterility*. Retrieved from: <https://www.asrm.org/>
- Bulun, S. E., Monsavaïs, D., Pavone, M. E., Dyson, M., Xue, Q., Attar, E., & Su, E. J. (2012). Role of estrogen receptor- β in endometriosis. In *Seminars in reproductive medicine* (Vol. 30, No. 01, pp. 39-45). Thieme Medical Publishers.
- Christ, J. P., & Cedars, M. I. (2023). Current Guidelines for Diagnosing PCOS. *Diagnostics* 2023, 13, 1113.
- ESHRE. (2023). International evidence-based guideline for the assessment and management of polycystic ovary syndrome (PCOS). Retrieved from: <https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Polycystic-Ovary-Syndrome>
- Eskandar, M., Al-Asmari, M., Sahra, M. (2025). Combination of letrozole and clomiphene citrate versus monotherapy for ovulation induction in PCOS: A randomized controlled trial. *Journal of Reproductive Medicine*, 70(2), 112–119.
- Franik, S., Eltrop, S. M., Kremer, J. A., Kiesel, L., & Farquhar, C. (2018). Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews*, (5).
- Gowri, V., Al-Amri, A., Almamari, T. M. A., Al Khaduri, M., & Jaju, S. (2022). The success of ovulation induction with letrozole and gonadotropins in obese and nonobese women: A study from a tertiary center. *International Journal of Reproductive Medicine*, 2022(1), 1931716.
- Gysler, M., March, C. M., Mishell, D. R., & Paulson, R. J. (1982). A normal dose of clomiphene citrate: Single versus multiple ovulations, conception rate, and pregnancy wastage. *Fertility and Sterility*, 37(5), 639–644.
- Legro, R. S., Arslanian, S. A., Ehrmann, D. A., Hoeger, K. M., Murad, M. H., Pasquali, R., & Welt, C. K. (2013). Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, 98(12), 4565-4592.
- Mejia, R. B., Summers, K. M., Kresowik, J. D., & Van Voorhis, B. J. (2019). A randomized controlled trial of combination letrozole and clomiphene citrate or letrozole alone for ovulation induction in women with polycystic ovary syndrome. *Fertility and sterility*, 111(3), 571-578.
- Miller, K. A. R., & Pinheiro, G. M. (2026). Comparative Outcomes of Letrozole Versus Clomiphene Citrate for Ovulation Induction in Patients With PCOS: Systematic Review and Meta-Analysis. *JBRA Assisted Reproduction*, 30(1), 146.
- Ministry of Health of the Republic of Indonesia. (2022). *Pedoman Nasional Pelayanan Kedokteran (PNPK)*. Retrieved from: <https://kemkes.go.id/id/media/subfolder/pedoman/pedoman-nasional-pelayanan-kedokteran-pnpk>
- National Institutes of Health. (2020). Infertility and women with PCOS: Clinical protocols and management. U.S. Department of Health and Human Services. Retrieved from: <https://www.nichd.nih.gov/health/topics/infertility>

Juwana Janu*, Reny Haryani

Institut Teknologi Sumatra

Corresponding author: * Email: juwana.janu@fa.itera.ac.id

DOI: 10.56922/mchc.v5i1.3084

Shifting the paradigm to letrozole as first-line ovulation induction in pcos: a review of efficacy and safety

- Permadi, I. W., & Prasetyaji, I. W. (2025). Breaking the cycle of infertility with clomiphene citrate and letrozole for successful ovulation induction for obese women with PCOS. *Majalah Obstetri & Ginekologi*, 33(1), 44-52.
- Wang, L., Lv, S., Li, F., Bai, E., & Yang, X. (2021). Letrozole versus clomiphene citrate and natural cycle: endometrial receptivity during implantation window in women with polycystic ovary syndrome. *Frontiers in endocrinology*, 11, 532692.
- Xia, H., Sun, X., Guan, H., Zhang, R., & Zhang, W. (2021). Identification of predictors of the ovarian response to clomiphene citrate in infertile women with polycystic ovary syndrome: a prospective cohort study. *Journal of International Medical Research*, 49(4), 03000605211000569.

Juwana Janu*, Reny Haryani

Institut Teknologi Sumatra

Corresponding author: * Email: juwana.janu@fa.itera.ac.id

DOI: 10.56922/mchc.v5i1.3084