



LITERATURE REVIEW

Meta-Analysis: Letrozole vs Clomiphene Citrate as Ovulation Induction in PCOS

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Objective: Polycystic Ovarian Syndrome (PCOS) is a prevalent endocrine disorder in women of reproductive age, characterized by symptoms such as hyperandrogenism, irregular menstrual cycles, and polycystic ovaries. This systematic review and meta-analysis aim to evaluate the efficacy of Letrozole, an aromatase inhibitor, inducing ovulation compared to Clomiphene Citrate (CC) in women with PCOS

Method: Studies published between 2020 and 2024 were included, following PRISMA guidelines and utilizing the PICOS framework. Seven randomized controlled trials (RCTs) involving 1,037 women diagnosed with PCOS based on the Rotterdam criteria met the inclusion criteria

Result: The meta-analysis showed Letrozole had a slightly higher ovulation rate (68.5% vs. 60.5% for CC), though the difference was not significant (RR 1.13, 95% CI 1.00–1.28, $P = 0.06$, $I^2 = 10\%$). However, Letrozole significantly improved pregnancy rates (26.4% vs. 18.4% for CC; RR 1.42, 95% CI 1.02–1.99, $P = 0.04$, $I^2 = 0\%$);

Conclusion: The findings support Letrozole as a viable and potentially more practical option than Clomiphene Citrate for ovulation induction in women with PCOS, particularly in improving pregnancy rates. Future research should focus on optimizing treatment regimens and exploring long-term effects to further enhance fertility outcomes for this population.

Keywords: letrozole, aromatase inhibitor, clomiphene citrate, polycystic ovarian syndrome, ovulation induction.

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is a complex endocrine disorder prevalent among women of reproductive age, characterized by ovarian enlargement, excess androgen hormones, and insulin resistance.^{1,2} Symptoms include ovulatory dysfunction, infertility, acne, hirsutism, and obesity.^{3,4} Approximately 116 million women are affected globally, with a prevalence of 3.4%, according to the WHO. PCOS prevalence rates are higher in Denmark, Turkey, and Australia, reaching 15%-20%.⁵⁻⁸ The etiology of PCOS includes genetic and environmental factors, with genetic predisposition increasing the risk among those with a family history. Poor diet and inactivity can exacerbate the condition.⁹ Pathological processes involve hormonal dysfunction, insulin resistance, inflammation, and neuroendocrine disturbances, contributing to hyperandrogenism.^{10,11}

Diagnosis is based on modified Rotterdam criteria, requiring at least two features: hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology on ultrasound (USG). Hyperandrogenism can be confirmed through hormone levels and clinical assessments, while oligo-anovulation is indicated by irregular menstrual cycles. Ultrasound typically shows more than 20 follicles per ovary.¹²⁻¹⁴ PCOS accounts for about 70% of anovulatory infertility cases, affecting both ovulation and oocyte quality, complicating conception.^{15,16} Insulin resistance and hyperandrogenism also impact egg quality and the endometrial environment.¹⁷⁻¹⁹

Ovulation induction is a primary treatment for infertility, with Clomiphene citrate (CC) as the first-line therapy, achieving ovulation rates of 70-90%. However, CC may affect the endometrium and cervical mucus, reducing pregnancy success rates to about 30-40%.^{15,20,21} Letrozole, an aromatase inhibitor, offers a promising alternative for ovulation induction in PCOS by inhibiting the aromatase enzyme and increasing gonadotropin secretion. It has milder side effects and lower risks of multiple pregnancies compared to CC, achieving higher ovulation and pregnancy rates, particularly in women resistant to CC. Its use should be guided by evidence and clinical considerations.^{15,20,22}

METHODS

Search Strategy

This study employed a systematic review and meta-analysis design, following PRISMA guidelines and the PICOS framework. A comprehensive search was conducted across multiple databases, including PubMed, ScienceDirect, Wiley Online Library, EuropePMC, SageJournal, and Springer Link, for open-access, full-text journals published in English from 2020 to 2024. Boolean operators combined keywords such as "Aromatase Inhibitor," "Letrozole," "Ovulation," "Induction," "PCOS," and "Polycystic Ovary Syndrome." Studies were included if they were randomized controlled trials (RCTs) published within the specified period, in English, and involved PCOS patients diagnosed using the 2003 Rotterdam criteria. Primary outcomes assessed ovulation and pregnancy rates, time to ovulation, follicle count, endometrial thickness, and live birth rates, with secondary outcomes examining safety and side effects like ovarian hyperstimulation syndrome (OHSS). Studies

were excluded if infertility stemmed from causes other than PCOS, such as male infertility or other endocrine disorders (e.g., hyperprolactinemia), or if participants had a history of ovarian surgery, severe health conditions, non-adherence to treatment, uterine abnormalities, prior exposure to mutagens, or allergies to the study drugs.

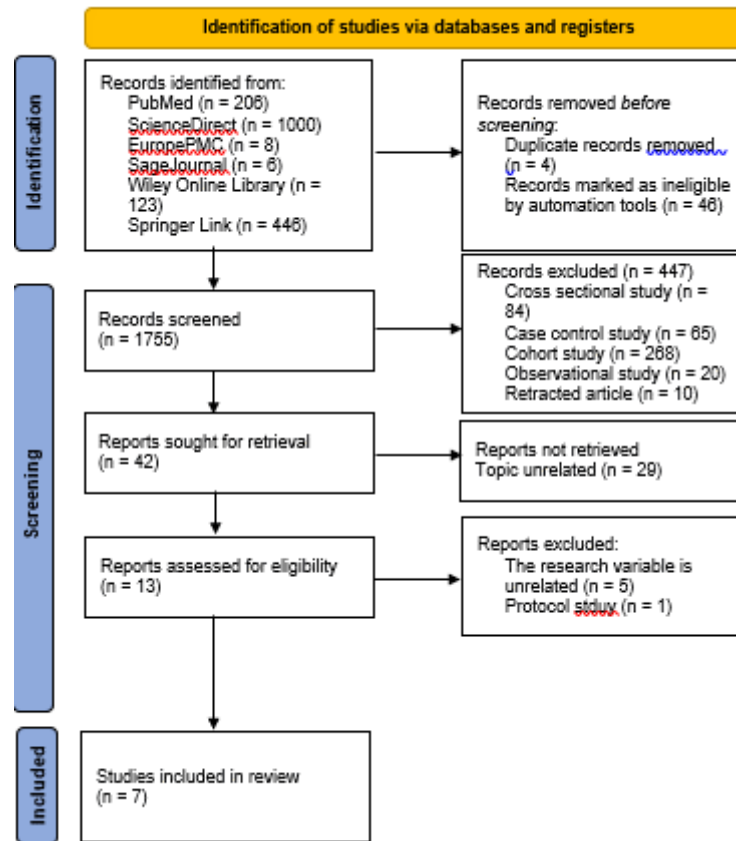


Figure 1. Flow diagram of the study selection, adaptation from PRISMA.²³

Statistics analysis

The study's quality was appraised using PRISMA guidelines and the Joanna Briggs Institute (JBI) methodology for systematic reviews of RCTs, with the risk of bias assessed through RevMan 5.4.1. During data extraction, authors independently selected databases, screened titles and abstracts, and reviewed full texts following the PICOS framework. Data from seven studies were extracted into tables, covering study characteristics such as authors, study types, subject details, interventions, and outcomes, with only the most recent or comprehensive data used. The systematic review followed JBI Critical Appraisal elements, and bias was assessed across five domains per the Risk of Bias 2.0 guidelines, using Review Manager for graphical analysis. High bias risk appeared in studies with non-blind interventions, affecting participants, providers, and assessors. Additionally, one study lacked a CONSORT diagram, and the volume of included studies impacted data integrity.

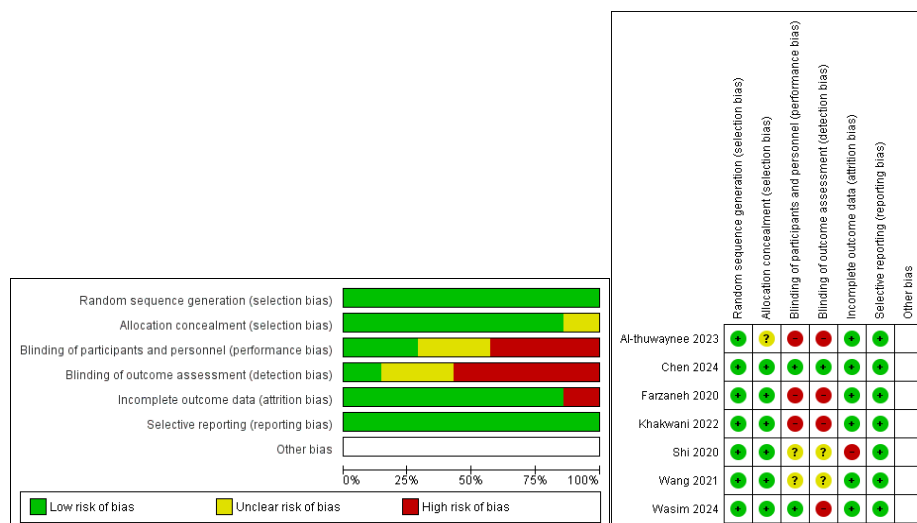


Figure 2. Risk of bias graph and risk of bias summary of the study selection using RevMan 5.4. High bias risk appeared in studies with non-blind interventions, affecting participants, providers, and assessors.²⁴

Study Assessment Results

Table 1. Study assessment results using JBI Critical Appraisal Tools.¹²

No	Citation	The Criteria of JBI Critical Appraisal													Result
		1	2	3	4	5	6	7	8	9	10	11	12	13	
1	(Al-Thuwaynee et al., 2023) ¹³	✓	-	✓	-	-	-	✓	✓	✓	✓	✓	✓	✓	69%
2	(Shi et al., 2020) ¹⁴	✓	✓	✓	-	-	-	✓	-	✓	✓	✓	✓	✓	69%
3	(Chen et al, 2024) ¹⁵	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
4	(Wang et al, 2021) ¹⁶	✓	✓	✓	-	-	-	✓	✓	✓	✓	✓	✓	✓	76%
5	(Khakwani et al, 2022) ¹⁷	✓	✓	✓	-	-	-	✓	✓	✓	✓	✓	✓	✓	76%
6	(Wasim et al, 2024) ¹⁸	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	✓	92%
7	(Farzaneh et al, 2020) ¹⁹	✓	✓	✓	-	-	-	✓	✓	✓	✓	✓	✓	✓	76%

The risk of bias was assessed using the JBI Critical Appraisal tool, with the JBI Checklist applied to RCTs, requiring a minimum score of 50% for inclusion. Studies scoring below this threshold were excluded to prevent bias. All included studies scored above 50%, with quality ratings from 69% to 100%, confirming they met quality standards for the review.

Meta-analysis

The meta-analysis used RevMan 5.4.1 software with a random-effects model to analyze dichotomous outcomes, presenting results as relative risk (RR) with a 95% confidence interval (CI) for both the control (clomiphene citrate) and intervention (letrozole) groups. Heterogeneity was

assessed using the chi-square test ($P \leq 0.10$ indicating significance) and quantified by the I^2 statistic to show the proportion of variation due to heterogeneity.

RESULT

Study Characteristics

A total of 1,037 women with PCOS were included in this review. All participants were diagnosed according to the Rotterdam 2003 criteria, were between 18 and 40 years of age, and had primary infertility. Across the included studies, participants generally had normal organ function and no history of ovarian surgery, endometriosis, or use of ovulation-inducing agents outside the study protocol.

The included studies evaluated several ovulation induction strategies. Four studies directly compared letrozole with clomiphene citrate (CC).^{26,29–31} Two of these studies used a stair-step protocol, in which treatment was started at a low dose for five days and follicular development was monitored by ultrasound. One study also incorporated lifestyle modification as part of the intervention. Other studies evaluated letrozole in comparison with human menopausal gonadotropin (HMG) or follicle-stimulating hormone (FSH). Treatment duration and monitoring differed slightly across studies, but ovulation and pregnancy were assessed as the main reproductive outcomes.

Table 2. Study characteristics of the selection study

No	Author (year)	Study design	Country	Disease characteristics	Patients	Outcome
1	Al-Thuwaynee, et al. (2023) ¹³	Randomized Controlled Trial (RCT)	Iraq	Polycystic Ovarian Syndrome (PCOS)	100 patient LTZ: 50 patient CC: 50 patient	LTZ showed a higher ovulation rate (86% vs. 72%) and a slight increase in pregnancy rate (22% vs. 18%) compared to CC, though not statistically significant. LTZ significantly shortened the time to ovulation (17.2 days vs. 24.1 days, $p < 0.001$) with no difference in adverse effects, indicating it is as safe as CC.
2	Shi et al. (2020) ¹⁴	RCT	Republic of China	PCOS	96 patient LTZ: 48 patient HMG: 48 patient	There were no significant differences between LTZ and HMG in ovulatory cycles (53.6% vs. 64.7%), pregnancy rates (22.9% vs. 27.1%), or miscarriage rates. However, HMG had more mature follicles ($P < 0.01$). LTZ showed fewer ovarian cysts ($P < 0.05$), and ovarian hyperstimulation was higher with HMG (12.5% vs. 2 cases in LTZ).
3	Chen et al. (2024) ¹⁵	RCT	Republic of China	PCOS	220 patient LTZ 2,5 mg + FSH	The cumulative pregnancy rate was higher in the LTZ 2.5 mg/FSH group compared to the 5

No	Author (year)	Study design	Country	Disease characteristics	Patients	Outcome
					: 110 patient LTZ 5 mg + FSH : 110 patient	mg/FSH group (72.7% vs. 59.1%, $p = 0.033$). Clinical pregnancy rates were also more significant for the 2.5 mg group (36.2% vs. 26.3%, $p = 0.021$), with no significant differences in ovulation rates or adverse effects.
4	Wang et al (2021) ¹⁶	RCT	Republic of China	PCOS	270 patient LTZ: 90 patient CC: 90 patient NC: 90 patient	Ovulation rates were similar between LTZ and CC groups ($P > 0.05$). However, LTZ showed better endometrial parameters and higher integrin avb3 and VEGF levels in uterine fluid compared to CC and natural cycles ($P < 0.05$). LTZ also had higher clinical and ongoing pregnancy rates than CC ($P < 0.05$).
5	Khakwani, et al (2022) ¹⁷	RCT	Pakistan	PCOS	78 patient LTZ: 38 patient CC: 38 patient	Among 70 patients who completed follow-up, efficacy was recorded in 23 (59.0%) patients in LTZ compared to 14 (35.9%) in CC ($p=0.0413$). The average endometrial thickness was significantly better in

No	Author (year)	Study design	Country	Disease characteristics	Patients	Outcome
6	Wasim, et al (2024) ¹⁸	RCT	Pakistan	PCOS	220 patient LTZ: 110 patient CC: 110 patient	LTZ compared to CC (8.1±1.5 mm vs. 6.8±1.9 mm, p=0.0022). LTZ showed better results compared to CC in pregnancy rates (29.0% vs. 15.4%, p=0.015), single follicle development (77.2% vs. 52.7%, p=0.000), and live birth rates (25.4% vs. 10.9%, p=0.005). Both groups had similar ovulation rates (68.1% vs. 63.6%), early miscarriage rates (3.6% vs. 4.5%), and twin pregnancy rates. No ectopic pregnancies or congenital disabilities were reported. CC had more hot flushes (31.8% vs. 12.7%), while LTZ was associated with higher fatigue (30.9% vs. 8.1%) and dizziness (21.8% vs. 10.0%), but all side effects were generally well tolerated.
7	Farzaneh, et al (2020) ¹⁹	RCT	Iran	PCOS	120 patient LTZ: 60 patient	There was no significant difference in average endometrial thickness between the groups.

No	Author (year)	Study design	Country	Disease characteristics	Patients	Outcome
					LTZ + DX: 60 patient	Pregnancy rates, however, were higher in the LTZ plus DX group (23%) compared to the LTZ group (8%), with a statistically significant difference ($p = 0.024$). The average follicle diameter showed no significant variation between the two groups.

CC = clomiphene citrate, LTZ = Letrozole, DX = dexamethasone, NC = natural cycle

Ovulation Rate

Four studies comparing letrozole and CC were included in the analysis of ovulation rate.^{26,29–31} Data from 289 participants showed an ovulation rate of 68.5% in the letrozole group and 60.5% in the CC group. Although ovulation occurred more frequently with letrozole, the pooled effect did not reach statistical significance (RR 1.13, 95% CI 1.00–1.28, $P = 0.06$).

Heterogeneity between studies was low ($\text{Chi}^2 = 3.33$, $I^2 = 10\%$, $P = 0.34$), indicating relatively consistent findings across the included studies.

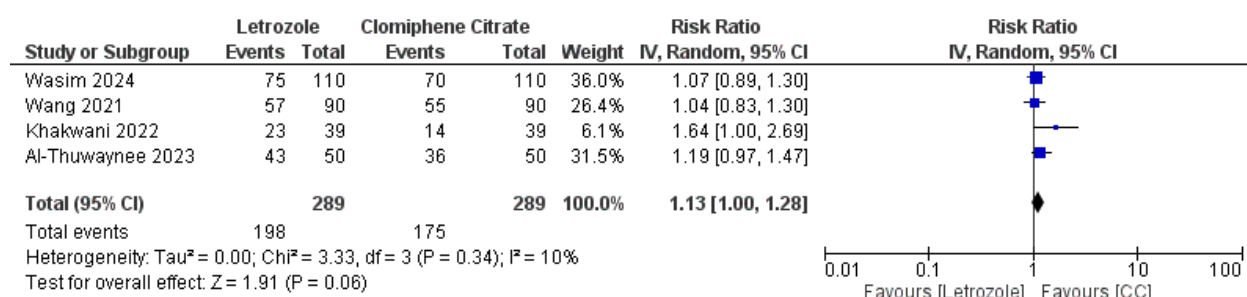


Figure 3. Forest plot analysis of ovulation rates showed that letrozole had a slightly higher ovulation rate (68.5% vs. 60.5% for CC), though the difference was insignificant (RR 1.13, 95% CI 1.00–1.28, $P = 0.06$, $I^2 = 10\%$).²⁴

Pregnancy Rate

Three studies reported pregnancy outcomes following ovulation induction with letrozole or CC.^{26,29,31} A total of 250 participants were analyzed in each treatment group. Pregnancy occurred in 26.4% of women receiving letrozole compared with 18.4% of those receiving CC.

The pooled analysis showed a significantly higher pregnancy rate with letrozole (RR 1.42, 95% CI 1.02–1.99, $P = 0.04$). No relevant heterogeneity was observed among the studies ($\text{Chi}^2 = 1.87$, $I^2 = 0\%$, $P = 0.39$).

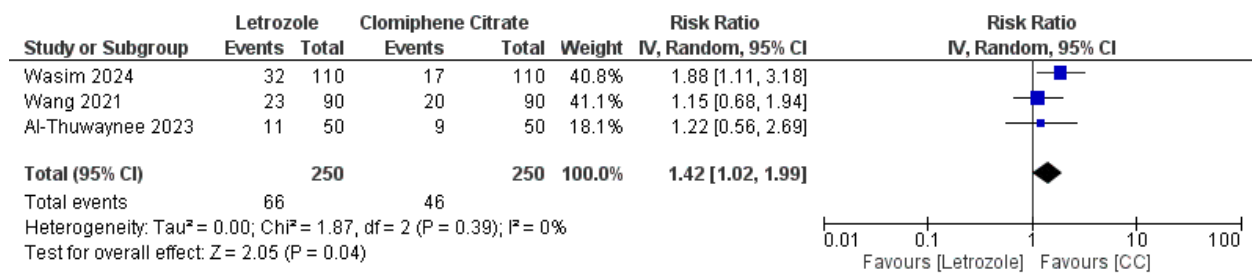


Figure 4. Forest plot analysis of pregnancy rates showed that letrozole significantly improved pregnancy rates (26.4% vs. 18.4% for; RR 1.42, 95% CI 1.02–1.99, $P = 0.04$, $I^2 = 0\%$).²⁴

DISCUSSION

Polycystic ovary syndrome is one of the most common causes of anovulatory infertility. Its clinical presentation is variable, but oligo-ovulation and anovulation are among the main reproductive problems encountered in women with PCOS.^{33,34} Clomiphene citrate has traditionally been used for ovulation induction in these patients. Although it is effective in stimulating ovulation, its anti-estrogenic activity may adversely affect the endometrium and cervical mucus, which may reduce the likelihood of implantation. It is also associated with an increased risk of multiple follicular development and multiple pregnancy.^{15,35,36}

Letrozole has increasingly been used as an alternative to CC. As an aromatase inhibitor, letrozole temporarily reduces estrogen synthesis without causing the prolonged anti-estrogenic effects typically associated with CC. This pharmacological difference may explain its relatively favorable effect on the endometrium and its lower tendency to produce multiple follicular development.^{37–39} The studies included in this review used letrozole doses ranging from 2.5 mg to 7.5 mg for five days, either alone or as part of a combined or sequential stimulation protocol.

The present meta-analysis showed that both letrozole and CC were effective in inducing ovulation. The ovulation rate was numerically higher with letrozole, at 68.5% compared with 60.5% with CC. However, the difference was not statistically significant. The effect estimate was also close to the threshold of significance (RR 1.13, 95% CI 1.00–1.28, $P = 0.06$). These findings suggest that the ability of letrozole to induce ovulation may be comparable to that of CC rather than clearly superior.

The findings were different when pregnancy rate was assessed. Pregnancy occurred more frequently in the letrozole group, and the pooled result reached statistical significance. Women treated with letrozole had a 42% higher relative likelihood of pregnancy than those treated with CC (RR 1.42, 95% CI 1.02–1.99). This result is in line with the meta-analysis by Imran, which also reported a higher pregnancy rate following treatment with letrozole.⁴⁰

The difference between ovulation and pregnancy outcomes is clinically relevant. Ovulation alone does not necessarily result in conception, as successful pregnancy also depends on endometrial receptivity, follicular quality, fertilization, and implantation. Therefore, the higher pregnancy rate observed with letrozole despite a similar ovulation rate may reflect differences in the reproductive environment created by the two drugs.

Several studies have suggested that letrozole may have a more favorable effect on endometrial development. Improvements in endometrial thickness, endometrial volume, and implantation-related biomarkers, including integrin $\alpha\beta 3$ and vascular endothelial growth factor, have been reported after letrozole administration.^{29,30,41} These findings may partly explain the higher pregnancy rates observed in women treated with letrozole. In contrast, the anti-estrogenic effects of CC may persist beyond the period of ovarian stimulation and may have a less favorable effect on the endometrium.

Letrozole is also more commonly associated with monofollicular development.^{27,31,42} This characteristic is particularly relevant in ovulation induction, as recruitment of fewer follicles may reduce the risk of multiple pregnancy without compromising the probability of conception. Thus, the reproductive benefit of letrozole may not be limited to its ability to induce ovulation, but may also relate to the quality of the follicular and endometrial response. Other treatment strategies have also been investigated in women who do not achieve an adequate response with oral ovulation induction alone. The addition of dexamethasone to letrozole has been reported to improve ovarian response and pregnancy outcomes in selected patients.^{37,43–45} Sequential treatment involving letrozole followed by gonadotropins has also been explored. Chen et al. reported that letrozole 2.5 mg followed by FSH produced a higher cumulative pregnancy rate than letrozole 5 mg followed by FSH (72.7% vs. 59.1%, $P = 0.033$).²⁸ The benefit was particularly evident in women older than 28 years and those with a BMI below 24 kg/m². These findings suggest that treatment response may depend not only on the choice of medication, but also on dose, sequence, and patient characteristics.

Safety remains an important consideration when choosing an ovulation induction regimen. Letrozole has been reported to have a lower risk of ovarian hyperstimulation and multiple pregnancy than some gonadotropin-based regimens. Shi et al. found that ovarian cyst formation and OHSS occurred less frequently in the letrozole group than in the HMG group, with a statistically significant difference.²⁷ When letrozole is compared directly with CC, however, the overall adverse-effect profiles appear broadly similar. Al-Thwaynee et al. and Wasim et al. reported no significant differences in the occurrence of nausea, vomiting, headache, or dizziness between the two treatments.^{26,31} Hot flushes and fatigue have been reported somewhat more often with letrozole, but these symptoms are generally mild and well tolerated. Overall, the findings of this review suggest that letrozole and CC are both effective options for ovulation induction in women with PCOS. Letrozole did not show a statistically significant advantage in ovulation rate, but it was associated with a significantly higher pregnancy rate. The more favorable endometrial response and tendency toward monofollicular development may contribute to this difference.

This review has several limitations. The methodological quality of the included studies was not uniform, and information regarding blinding was incomplete in several studies, resulting in an unclear risk of bias in some domains. There were also differences in treatment doses, stimulation protocols, additional medications, and monitoring methods across studies. Although statistical heterogeneity was low in the pooled analyses, these clinical differences should still be considered when interpreting the findings. Critical appraisal of each included study was therefore performed to reduce the potential influence of methodological bias.

CONCLUSION

Polycystic Ovarian Syndrome (PCOS) disrupts ovulation and reduces fertility in women. While Clomiphene Citrate (CC) has been the standard treatment for inducing ovulation, Letrozole is emerging as a potentially more effective option, especially for improving pregnancy rates. Studies show that Letrozole and CC yield similar ovulation rates. Still, Letrozole may offer a slight advantage in achieving pregnancy, making it a promising choice for women with PCOS seeking to conceive. However, due to limited study numbers and mixed results, further large-scale randomized trials are needed to confirm long-term outcomes and refine treatment strategies for fertility in PCOS.

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