META-ANALYSIS

Breaking the cycle of infertility with clomiphene citrate and letrozole for successful ovulation induction for obese women with PCOS

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ABSTRACT

Objective: Indonesia has a higher prevalence of PCOS, a common endocrine disorder that affects 4% to 8% of women who are of reproductive age. Obesity, insulin resistance, and anovulatory infertility are all linked to PCOS. The ability of letrozole and clomiphene citrate (CC) to induce ovulation in overweight or obese PCOS patients was examined in this meta-analysis.
Materials and Methods: PRISMA criteria were followed when conducting a systematic literature search utilizing PubMed, Google Scholar, Cochrane Library, and ScienceDirect. Keywords included PCOS, obesity, clomiphene, and letrozole. Studies published between 2000 and 2024 in English, with full-text accessibility, were included. The search yielded 260 studies, of which nine were selected for quantitative synthesis.
Results: Letrozole showed a 12% increase in ovulation and a 33% increase in pregnancy rates compared to clomiphene citrate (CC). There was no discernible difference in the two groups' endometrial thickness. This meta-analysis finds that letrozole is more successful than CC in triggering ovulation and achieving conception in overweight or obese PCOS patients.
Conclusion: In women with PCOS who are overweight or obese, letrozole works better than clomiphene citrate (CC) to induce ovulation. Because it is accessible and reasonably priced, CC is still the first-line treatment, even if its efficacy is lesser. As a second-line therapy, letrozole is advised for women who are resistant to or do not react to CC.

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Highlights:

1. Polycystic ovarian syndrome (PCOS) is a hyperandrogenous state with oligo-anovulation.
2. Letrozole is more efficient than CC in promoting ovulation and facilitating pregnancy in women with PCOS who are overweight or obese.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a hyper-androgenous state with oligo-anovulation that cannot be explained by another disorder.[1,2] It affects about 1 in 10 women before menopause and struggles with its complications.[3] PCOS is a common endocrinopathy that affects 4%-8% of women of childbearing age, with Indonesia reporting 5-10% prevalence.[4,5] The exact etiology and pathophysiology of PCOS remain largely unknown. However, data points to several internal and external factors, such as genetics, epigenetics, environmental factors, insulin resistance, and hyper-androgenism.[6]

Letrozole, compared with clomiphene citrate, demonstrated a higher live birth rate in overweight and obese PCOS patients. Letrozole's ability to gradually reduce estrogen levels causes an increase in follicle-stimulating hormone (FSH). Compared with clomiphene citrate, which is associated with an increased incidence of thin endometrium, this mechanism increases the ovulation rate and endometrial receptivity. In addition, letrozole showed better performance in cases of clomiphene resistance by improving ovulation and pregnancy. In a randomized controlled trial, letrozole increased ovulation rates by 75% in clomiphene-resistant women, surpassing the performance of other alternative therapies. Letrozole also has milder side effects, such as hot flashes and mood changes, which makes it a safer choice for long-term use.

To overcome PCOS, the most crucial step is to lose at least 5% of body weight, which can be achieved through regular exercise, a fat and sugar-free diet, or using complementary and alternative medicine strategies.[7,8] Cardiometabolic dysfunction is associated with most comorbidities connected to obesity, such as type 2 diabetes, hypertension, and other symptoms of metabolic syndrome.[7,9] Insulin resistance, compensatory hyperinsulinemia, and underlying cardiometabolic dysfunction are also linked to obesity-related cancers, including endometrial carcinoma.[10]

Clomiphene citrate (CC) and letrozole help induce ovulation in PCOS patients. CC is adequate for most drugs, but letrozole shows a higher success rate, especially in clomiphene-resistant patients. Letrozole also has fewer side effects and better results, making it a safer and more practical choice for women with PCOS.

One of the main complaints that most patients see a health professional is a complaint related to infertility.[11] About 25% of couples have infertility due to ovulation disorders, and PCOS is the primary cause of an-ovulatory infertility, which accounts for over 70% of all instances.[12,13] Several endocrine and metabolic traits, including an elevated risk of cardiovascular disease, type 2 diabetes mellitus, dyslipidemia, obesity, insulin resistance, and hyperinsulinism, are also associated with PCOS. Additionally, miscarriages and pregnancy problems like gestational diabetes may be more common in women with PCOS.[14]

For PCOS patients, ovulation induction is the primary treatment option for anovulatory infertility.[15] Clomiphene citrate, an effective selective modulator of estrogen receptors, is used in infertile PCOS patients.[15,16] However, only 18-20% of women who use clomiphene citrate become pregnant, and ovulation rates range from 60-85%.[17,18] Women with PCOS who are overweight and obese often show more severe insulin resistance and hyperandrogenism compared with lean PCOS cases, which can affect ovulation and fertility outcomes. Body weight is essential in transmitting the effectiveness of treatment for these metabolic and hormonal problems. In addition, obesity-induced inflammation and altered adipokine profiles may impair endometrial receptivity and its response to ovulation induction therapy. Therefore, paying special attention to women who are overweight or obese makes it possible to launch treatment methods that are more targeted and adapted to their specific problems.

Letrozole, an aromatase inhibitor, has been used as a backup medication option for PCOS patients, particularly those who become resistant to clomiphene.[19] This meta-analysis aims to analyze and compare the efficacy of clomiphene citrate and letrozole regarding infertility in overweight and obese PCOS patients.

MATERIALS AND METHODS

Search strategy

The 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) standards were followed in conducting and presenting this meta-analysis. The literature was thoroughly searched using PubMed, Google Scholar, Cochrane Library, and ScienceDirect. "(PCOS OR Polycystic Ovary Syndrome) AND (Obese OR Obesity OR Overweight) AND (Clomiphene OR Clomiphene citrate) AND (Aromatase Inhibitor OR Letrozole)" were the predefined keywords used to perform the literature search. Papers with pertinent titles and abstracts will be considered for further qualitative and quantitative analysis and full-text evaluation throughout this process. Studies that were published between 2000 and 2024, written in English, and had full-text accessibility are

included in this study. The specifics of the study search method are displayed in Figure 1.

Inclusion and exclusion criteria

Finding studies that provide specific information on the reproductive result of obese or overweight PCOS patients taking letrozole or clomiphene citrate was the main objective of the research selection criteria. Only studies that met these requirements were taken into consideration for inclusion to guarantee a thorough examination of the relative effectiveness of letrozole vs. clomiphene citrate for obese or overweight PCOS patients. To ensure the authenticity and dependability of the findings, the following exclusion criteria were used: 1) research that did not provide significant findings; 2) publications with full texts that are no longer accessible.

Data extraction and risk of bias assessment

The study's design, ovulation and pregnancy rates, treatment strategies, endometrial thickness, author name, and year of publication were all retrieved. After that, we took data out of the publications we had chosen. CONSORT (Consolidated Standards of Reporting Trials) was another tool used to evaluate the quality of articles about randomized-controlled trials. Every reviewer worked together to analyze the quality until an agreement was achieved.

Outcome measure

The key outcome indicators are the comparisons between ovulation rate, pregnancy rate, and endometrial thickness in each group. Relative risk (RR) and mean difference (MD) were computed with 95% confidence intervals to evaluate these results and thoroughly compare the two interventions.

Data analysis

Data analysis was performed using SPSS to ensure accuracy and reliability. A random-effects model based on the DerSimonian and Laird technique was used since the study populations can differ. There were two phases in the analysis. All continuous variables were first calculated for the mean difference (MD), RR, and 95% confidence interval (CI). The standard errors (SE) of the pertinent SMDs were then computed. A forest plot was used to graphically represent each study's MDs, RRs, and 95% CIs, giving researchers a thorough understanding of effect sizes and variability. The forest plot also includes the pooled MD, RR, and 95% confidence interval from the random-effects model to summarize the total effect estimate overall included trials. Using the Higgins I-squared (I2) statistical model, heterogeneity was investigated. The findings of the heterogeneity test were classified as minimal (0-25%), low (25%-50%), moderate (50-75%), or high (<75%).

RESULTS AND DISCUSSION

Included studies

The initial search turned up 260 studies from all databases. As many as 236 of the abstracts and titles were rejected after screening. Furthermore, four of them were eliminated because they were duplicates. Eleven further studies were eliminated since their findings had nothing to do with the review. Nine papers were ultimately considered for quantitative synthesis. The results of the qualitative synthesis of every study that was included are displayed in Table 1.

Study characteristics and outcomes

Table 1 displays the key characteristics of the included papers in this systematic review. Out of all the included research, the study with the lowest determined CONSORT score (19.00/25.00) had the lowest risk assessment. This suggests that more than two-thirds of the criteria were met by all the included studies, indicating a decreased chance of bias and generally excellent quality.

Ovulation rate

Figure 2 presented the relative risk of the ovulation rate between the CC and letrozole groups. We found that the RR of the ovulation rate in the letrozole group was significantly higher, specifically, 12% higher overall in comparison to the CC group with an RR of 0.88 (95% CI 0.84-0.93; $p < 0.0001$) with low heterogenicity showed by an I2 of 49%.

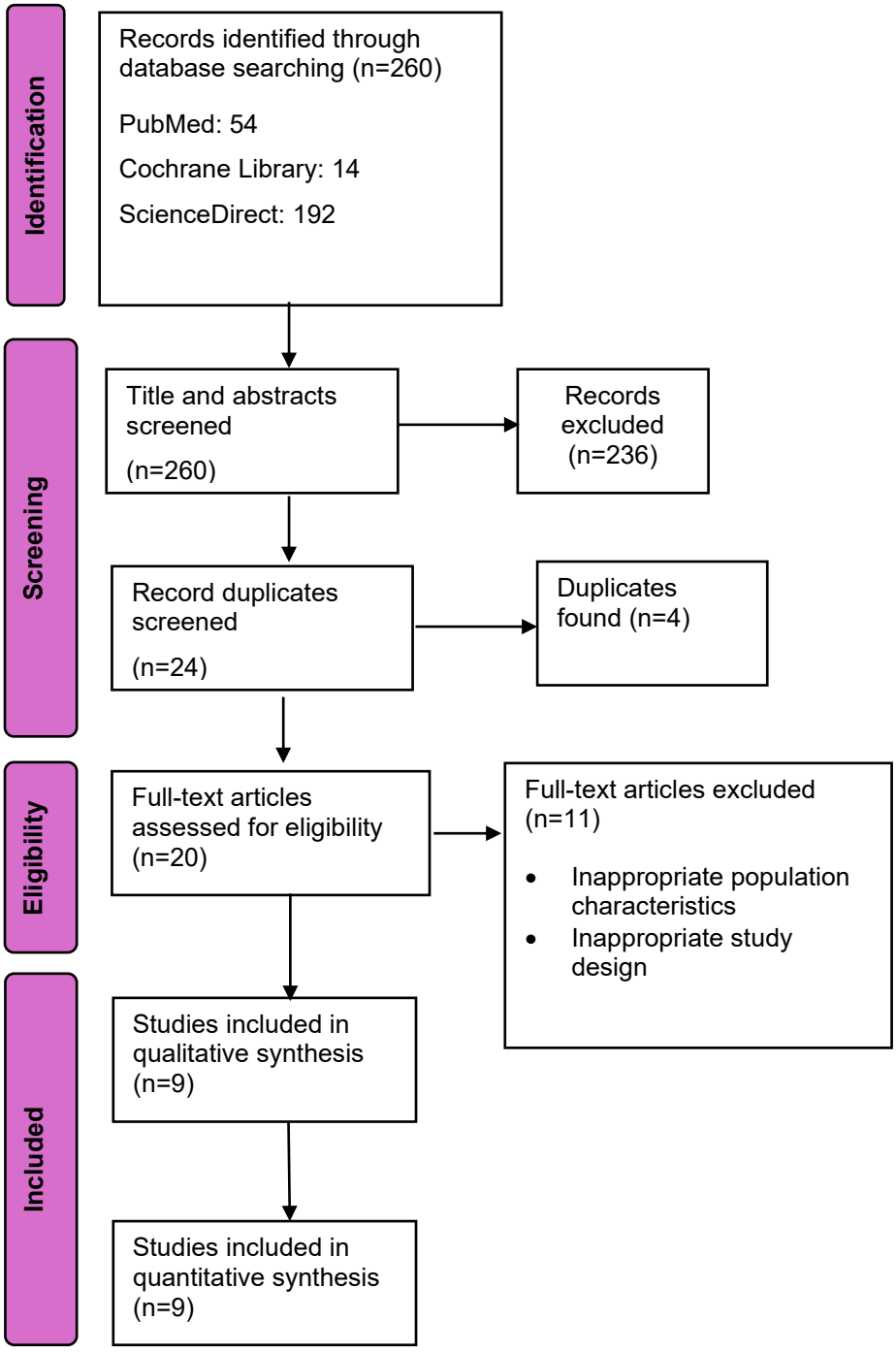

Figure 1. Flow diagram of literature search strategy for this meta-analysis

Table 1. Study characteristics

Authors	Year	Study design	CC group (n)	Letrozole group (n)	Clomiphen citrate group	Letrozole group	Ovulation		Pregnancy		Endometrial thickness	
							CC	Letrozole	CC	Letrozole	CC	Letrozole
Ray, et al.[19]	2012	RCT	78	69	100 mg	2.5 mg	48	60	14	20	8.78 ± 1.16	8.72 ± 1.41
Basakarod, et al.[20]	2023	RCT	40	40	50 mg	2.5 mg	16	22	3	8	8.45 ± 1.53	9.85 ± 2.32
Roy, et al.[21]	2012	RCT	106	98	50 mg	2.5 mg	72	65	28	43	6.3 ± 1.1	9.1 ± 0.3
Kar, et al.[22]	2012	RCT	51	52	100 mg	5 mg	31	38	4	12	7.65 ± 2.1	7.61 ± 1.96
Nambiar, et al.[23]	2018	RCT	96	104	100 mg	2.5 mg	89	102	51	57	10.53 ± 3.27	10.52 ± 2.79
Legro, et al.[24]	2014	RCT	376	374	50 mg	2.5 mg	288	331	81	117	10.1 ± 3.7	9.2 ± 3.8
Bigawy, et al.[25]	2008	RCT	34	30	150 mg	2.5 mg	25	24	5	5	6.43 ± 1.85	9.44 ± 1.81
Arya, et al.[26]	2021	RCT	313	314	50 mg	2.5 mg	Not reported		51	81	Not reported	
Wasiim, et al.[27]	2024	RCT	110	110	50 mg	2,5 mg	70	75	17	32	Not reported	

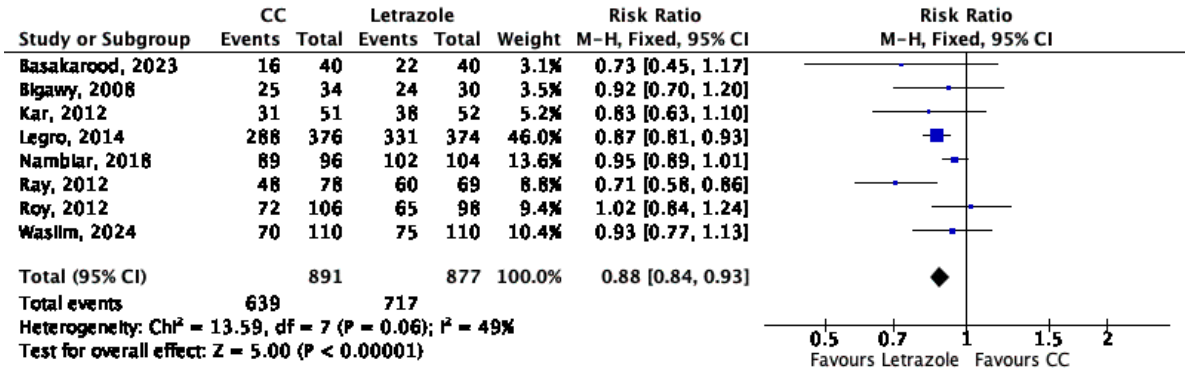

Figure 2. Pooled result of ovulation rate between CC vs letrozole

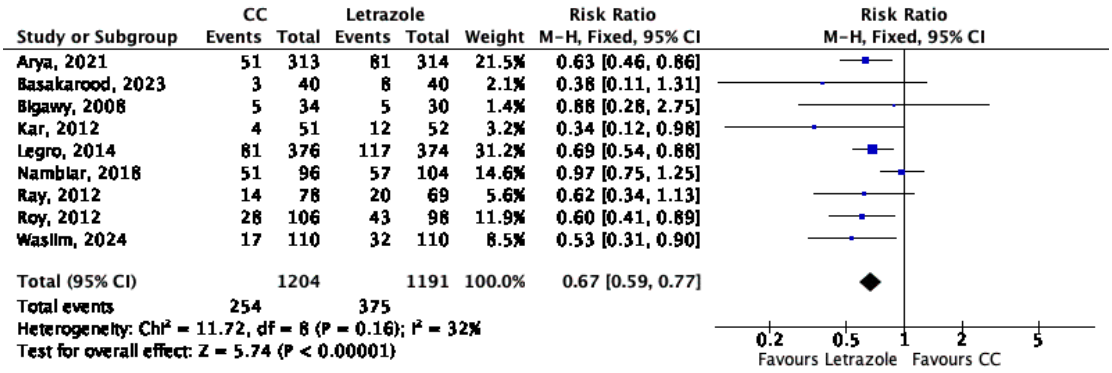

Figure 3. Pooled result of pregnancy rate between CC vs letrozole

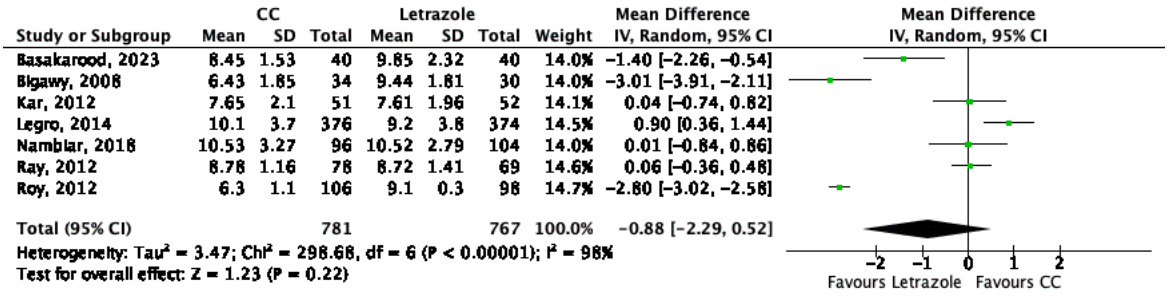

Figure 4. Pooled result of endometrial thickness between CC vs letrozole

Pregnancy rate

Figure 3 presented the relative risk of the pregnancy rate between the CC and letrozole groups. We found that the RR of the pregnancy rate in the letrozole group was significantly higher, specifically, 33% higher overall in comparison to the CC group with an RR of 0.67 (95% CI 0.59-0.77; p < 0.0001) with low heterogenicity showed by an I2 of 32%.

Endometrial thickness

Figure 4 presented the mean difference in endometrial thickness between the CC and letrozole groups. We found that the MD of the endometrial thickness between both groups was not significantly different with an MD of -0.88 (95% CI -2.29 - 0.52; p = 0.22) with high heterogenicity showed by an I2 of 98%.

According to our meta-analysis, letrozole was the best medication for ovulation induction in overweight or obese women with PCOS who were infertile or subfertile in terms of ovulation and pregnancy rate. However, there was no discernible difference between the two groups' endometrial thicknesses.

To induce ovulation, clomiphene citrate (CC) remains the main medication for infertile women with PCOS.[28] By inhibiting the brain's estrogen receptors via a negative feedback mechanism, CC, an anti-estrogen therapy, promotes the growth of follicles. By blocking the hypothalamic estrogen receptors, CC acts as an anti-estrogen, increasing the amplitude of pulses that release gonadotropin-releasing hormone (GnRH). The anterior pituitary's (LH) enhanced synthesis of follicle-stimulating hormone (FSH) and luteinizing hormone helps the follicles reach their final maturity. Using ultrasound and endocrine blood tests, CC administration should be monitored to determine the day of ovulation and prevent multiple pregnancies (risk rate of 11%).[19] As a monitoring technique, an ultrasound examination is performed on days 11 to 14, and measurements of follicular growth and endometrial thickness are also taken.[29]

The anti-estrogenic actions may also impact the endometrium and cervical mucus, which may reduce endometrial growth and impede implantation. Hot flushes, nausea, breast soreness, dizziness, and impaired vision are among the side effects of CC. Starting on days 2 through 5 of a cycle, the standard course of therapy is a daily dosage of 50 mg. Pregnancy rates are

only 30% to 40%, even though 70% to 90% of patients experience ovulation induction with CC.[30] Because twin and triplet pregnancies with CC are rising (5%–7% and 0.3%, respectively), ultrasonographic surveillance should be carried out to identify multi follicular development. Kafy and Tulandi noted this.[31] To increase ovulation and conception rates, women with PCOS who have anovulatory infertility and no other infertility problems should consider using CC as a second-line treatment (conditional recommendation based on evidence, lower quality of evidence).[32]

Letrozole is an aromatase inhibitor. Aromatase inhibitors produce lower levels of E2. This dramatically reduces the likelihood that many follicles will grow. Among CCs, this is one of the key benefits of letrozole. Letrozole also has the advantage of not interfering with endometrial estrogen receptors, which means it has no detrimental effects on cervical mucus or endometrial thickness. Letrozole may increase ovulation rates, as shown by Mejia et al. However, there is no proof that this medication increases the likelihood of getting pregnant. Letrozole is still advised as a second-line therapy for women with CC resistance or failure when no other reproductive problems are present.[33]

Letrozole's effectiveness in inducing ovulation in women who did not react well to CC was first shown by Mitwally and Casper in 2001.[33] In a recent review by Cochrane, Franik et al. discovered that letrozole showed a greater live birth rate than CC, according to evidence of moderate quality. Based on high-quality data, they also found that letrozole and CC had comparable rates of ovarian hyperstimulation syndrome (OHSS) and no differences in miscarriages or multiple pregnancies. Furthermore, letrozole seemed to reduce the chance of multiple pregnancies in comparison to CC, which had the most significant incidence of mono-follicular development.[16]

Typically, patients get 2.5 mg daily for five days, from day two to day five of the cycle (either naturally occurring or caused by progesterone). Follicle tracking with ultrasonography is used to track ovulation. Human chorionic gonadotropin (hCG) can induce ovulation and timed sexual activity when the leading follicle reaches a minimum of 18 mm. The estimated time frame for ovulation is 36 to 48 hours following stimulation. It is advisable to counsel couples who have more than two mature follicles to refrain from unprotected sexual activity. The dose may be increased by twice in the following cycle if ovulation is not achieved.[34]

Letrozole's ability to successfully induce ovulation has been explored in assisted reproduction, including intrauterine insemination (IUI) and in vitro fertilization methods.[31] In addition to causing ovulation in cases of anovulatory infertility, patients with unexplained infertility undergoing superovulation and IUI found that a prolonged letrozole regimen was more effective than clomiphene citrate.[32] To facilitate ovulation in women diagnosed with PCOS, letrozole has been compared to recombinant FSH and has proven to be an appropriate and affordable inducing drug. Based on prior research and the findings of this investigation, letrozole appears to be a viable substitute for clomiphene citrate in overweight or obese PCOS patients with anovulation-related infertility. It can be taken as a first-line medication to treat anovulation and stimulate the ovaries.

CONCLUSION

According to these results, letrozole is more efficient than CC in promoting ovulation and facilitating pregnancy in women with PCOS who are overweight or obese. However, it is important also to note that CC remains the first-line ovulation induction drug for PCOS patients due to its affordability, accessibility, and oral administration. For women who have either acquired resistance to clomiphene citrate (CC) or have not reacted to it, letrozole is recommended as a second-line treatment.

DISCLOSURES

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Conflict of interest

We have no conflict of interest to declare

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Author contribution

The authors contributed equally as first authors, involving in all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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