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LETROZOLE COMPARED WITH CLOMPIHENE CITRATE FOR POLYCYSTIC OVARIAN SYNDROME : A SYSTEMATIC REVIEW

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Abstract

According to the Consensus on the Management of PCOS, polycystic ovary syndrome, is an endocrine condition that produces oligo-anovulation, clinical and biochemical symptoms of hyperandrogenism, and distinctive ovarian morphological characteristics on ultrasonographic examination. PCOS is also associated with a higher risk of endometrial cancer. Both hyperandrogenism and anovulation are difficult conditions to manage. PCOS women often have higher GnRH pulsatility, which in turn causes increased pituitary LH secretion and an elevated LH/FSH ratio. Granulosa cells are responsible for the conversion of androgens to estrogen and the maturation of follicles, while LH is responsible for promoting androgen synthesis in theca cells. Intraovarian androgens produce atresia in later antral stages, although they do boost initial follicle recruitment by increasing preantral and early antral follicle growth. In contrast to CC on its own, letrozole was shown to increase the number of live births, and the overall level of evidence was moderate. There was insufficient evidence that there was a difference in the rate of live births between CC plus metformin and CC alone, and the overall certainty of the evidence was poor due to the risk of bias and imprecision. When contrasted with the use of CC by itself, the potential benefit of CC in combination with metformin was more apparent in women whose baseline blood insulin or HOMA-IR values were higher than average. In comparison to clomiphene citrate, letrozole was related with higher rates of ovulation, pregnancy, and successful delivery of a live baby. Despite the fact that the quality of the data is inconsistent, one study recommends letrozole over clomiphene citrate as an ovulation induction medicine for women who have infertility and PCOS.

Keyword: *Clompihene Citrate; Letrozole; Ovulation; Polycystic Ovarian Syndrome (PCOS)*

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) according to the Consensus on the Management of Polycystic Ovary Syndrome is an endocrine disorder that causes oligo-anovulation, clinical and biochemical signs of hyperandrogenism and special ovarian morphological signs on ultrasonographic examination.[1] According to The International Evidence Based Guideline For The Assessment and Management of Polycystic Ovary Syndrome, PCOS is the most common chronic anovulation disorder in women of reproductive age.[2] The incidence of PCOS varies widely depending on the population and diagnostic criteria.[3]

Most of the PCOS studies looked at the age group between 18 and 45 years. Meanwhile, the incidence of PCOS in reproductive women is 10-15%. PCOS occurs as a result of the interaction between three factors, namely ovarian factors, the hypothalamus-pituitary axis, to impaired insulin activity, which interact with each other in regulating ovarian function. The condition of Functional Ovarian Hyperandrogenism (FOH) has hyperinsulinism, resistance to insulin, which worsens the condition of hyperandrogenism and plays a role in the pathophysiology of PCOS.[4,5]

The condition of ovarian hyperandrogenism in PCOS causes the main clinical features of PCOS including hyperandrogenemia, oligo-anovulation and polycystic ovary features. Management of women with PCOS can be done with lifestyle modifications and medication.[6] Evaluation of HbA1c levels in patients with PCOS is a useful and indispensable approach for detecting the hyperglycemia that is frequently associated.[7] For a fairly long time, clomiphene citrate (CC) has been the standard drug for ovulation induction in patients with PCOS.[8]

Clomiphene citrate has a 35%–40% pregnancy rate despite an 85% ovulatory rate. The peripheral anti-estrogenic effects and two-week half-life of CC may explain this discrepancy between higher ovulation rates and lower conception rates. This slows endometrial growth.[9] Letrozole has been used to induce ovulation since 2001. Letrozole reduces estrogen production and levels. This frees the hypothalamic-pituitary axis from estrogens, increasing FSH. Since it doesn't affect endometrial, letrozole may be a better ovulation inducer. Its 48-hour half-life allows estrogen to peak later. This improves endometrial and pregnancy rates.[10]

Letrozole and clompihene citrate are two treatments for polycystic ovarian syndrome that are the focus of this investigation.

METHODS

The author of this study made certain that it complied with the prerequisites by referring to the recommendations provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. This is done in order to guarantee that the findings of the investigation are accurate. This review compare letrozole with clompihene citrate for polycystic ovarian syndrome. This is accomplished by evaluating or analyzing previous research on the topic. The purpose of this essay is to emphasize the significance of the issues discussed.

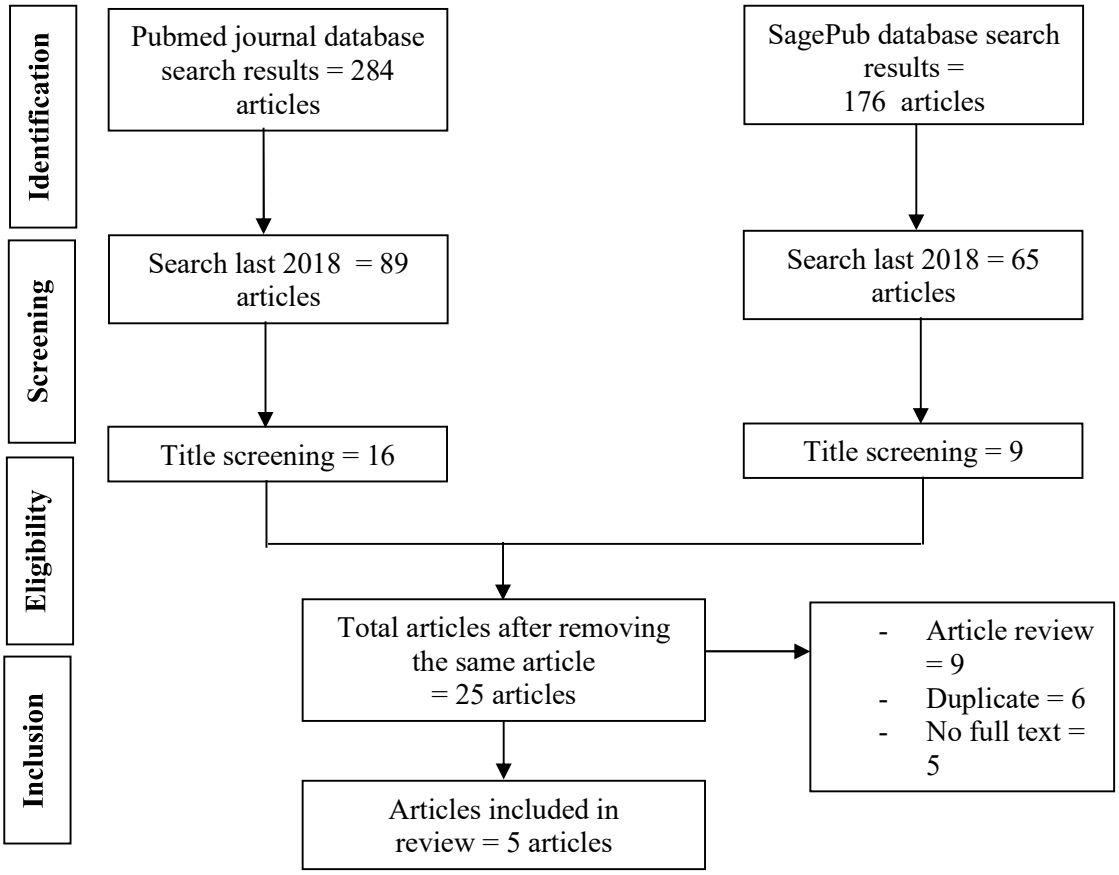

Figure 1. Article search flowchart

In order to take part in the investigation, researchers had to demonstrate that they satisfied the following requirements: 1) In order for the manuscript to be considered for publication, it needs to be written in English and the primary focus needs to be on contrasting the efficacy of letrozole with clomifene citrate in treating polycystic ovary syndrome. 2) This assessment takes into account works that were published after 2018, but before the time period that is being considered. Examples of research that is not acceptable for publication include editorials, submissions that do not include a DOI, already published review articles, and entries that are almost identical to previously published journal papers.

We used "letrozole"; "clompihene citrate" and "polycystic ovarian syndrome" as keywords.The search for studies to be included in the systematic review was carried out from May, 24th 2023 using the PubMed and SagePub databases by inputting the words: *("letrozole"[MeSH Terms] OR "letrozole"[All Fields] OR "letrozol"[All Fields]) AND ("clomiphene"[MeSH Terms] OR "clomiphene"[All Fields] OR ("clomiphene"[All Fields] AND "citrate"[All Fields]) OR "clomiphene citrate"[All Fields]) AND ("polycystic ovary syndrome"[MeSH Terms] OR ("polycystic"[All Fields] AND "ovary"[All Fields] AND "syndrome"[All Fields]) OR "polycystic ovary syndrome"[All Fields] OR ("polycystic"[All Fields] AND "ovarian"[All Fields] AND "syndrome"[All Fields]) OR "polycystic ovarian syndrome"[All Fields])* used in searching the literature.

The writers determined the eligibility of each study based on its abstract and title. They then turned to historical texts. This result was obtained after numerous investigations using the same pattern. Contributions in English must be unpublished. The systematic review included only eligible studies. This narrows down search results. Unsatisfactory research results are not investigated. The analysis will come later. Names, authors, publication dates, location, study activities, and parameters were all exposed in the paper. Endnote deleted duplicate articles from the search results. The titles and abstracts of relevant papers were examined by two reviewers.

Their whole texts were first reviewed for eligibility and data extraction. Review articles, animal studies, conference papers, and research on GWG and other health issues. The reviewers reached a consensus during their conversation. Before deciding which papers to investigate further, each author conducted their own examination of the studies mentioned in the title and abstract of each publication. Then, we will examine all papers that match the review's inclusion criteria and are thus good enough to be included. Then, based on what we've learned, we'll pick which papers to include in the review. This is how the papers to be evaluated are selected, as well as which papers to examine.

RESULT

Khakwani, et al (2022) conducted a study. It was found that the average age was 25.41 ± 2.84 years. Most of the patients, 51 of them (65.4%), lived in rural areas. 52 (66.7%) of the patients had a BMI of less than 25 kg/m2. Overall, the average length of not being able to have children was found to be 2.62 ± 0.74 years. Out of the 70 patients who finished the follow-ups and were looked at for effectiveness, 23 (59.0%) in Group-LE and 14 (35.9%) in Group-CC showed effectiveness (p = 0.0413). The average thickness of the endometrium was much greater in Group LE than in Group B (8.1 ± 1.5 mm vs. 6.8 ± 1.9 mm, p = 0.0022).

Bansal, et al (2021)[11] showed mean endometrial thickness was 9.86 ± 2.32 mm with letrozole and 9.39 ± 2.01 mm with CC (P = 0.751). The cumulative ovulation rates for letrozole and CC were 86.7% and 85.2%, respectively (P = 0.751). 42.2% of women in the letrozole group became pregnant, compared to 20% of women in the CC group (P = 0.04). In 68.4% of ovulatory cycles in the letrozole group compared to 44.5% in the CC group, monofollicular development was observed (P = 0.000). With letrozole, the mean time to obtain pregnancy was significantly shorter (log rank P = 0.042) than with CC (11.07 weeks).

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Khakwani, 2022[12]	Pakistan	Randomized controlled trial (RCT)	78 patients	It was discovered that letrozole had much superior efficacy than clomiphene citrate in inducing ovulation in women with anovulatory PCOS when compared to the other medication, clomiphene citrate.
Bansal, 2021[11]	India	Randomized controlled trial (RCT)	205 patients	In anovulatory women with PCOS, letrozole is a superior choice for inducing ovulation since it increases the likelihood of a successful pregnancy, decreases the amount of time it takes to conceive, and reduces the risk of having multiple children as a result of its high monofollicular development.
Wang, 2020[13]	China	Randomized controlled trial (RCT)	270 patients	PCOS women have greater endometrial receptivity during the implantation window of LE compared to CC, which may be connected to higher clinical pregnancy and continuing pregnancy rates. It's possible that endometrial FI measured with 3-D power Doppler and integrin v3 found in uterine secretory during the implantation window are the best non-invasive pregnancy predictor markers to use.
Mejia, 2019[14]	United State od America (USA)	Randomized controlled trial (RCT)	70 patients	When compared with letrozole on its own, the combination of letrozole and CC in women with infertility and PCOS was associated with a greater ovulation rate than letrozole on its

				own. To properly analyze the impact on the number of live births, additional research is required.
Al-Obaidi, 2019[15]	Iraq	Randomized controlled trial (RCT)	80 patients	Clomiphene citrate daily increased dominant follicle and oestradiol levels. Letrozole increased endometrial thickness more than clomiphene citrate. Letrozole and pregnant women had lower resistance and pulsatility indices than clomiphene citrate and non-pregnant groups.

Other study showed LE and CC had similar ovulation rates (P >0.05). The LE group had higher uterine fluid VEGF, integrin αvβ3, and endometrial ultrasonic parameters than the CC and natural cycle groups (P <0.05). LE had greater clinical pregnancy and continued pregnancy rates than CC (P <0.05). All pregnancy groups had higher endometrial ultrasonic parameters (VI, FI, and VFI), integrin αvβ3, and VEGF concentrations in uterine fluid than the no pregnancy group (P<0.05), and ongoing pregnancy had higher parameters than biochemical pregnancy.[13]

Mejia, et al (2019)[14] conducted a study with seventy patients were randomly assigned to receive either letrozole alone or letrozole and CC. The results were analyzed using the principle of intention to treat. Women who received letrozole and CC had a significantly higher ovulation rate than those who received letrozole alone (27 of 35 women [77%] vs. 15 of 35 women [43%]). In neither group were there any significant adverse events or multiple-gestation pregnancies. The profile of adverse effects was comparable between the two treatment groups.

Al-Obaidi, et al (2019)[15] compared with the letrozole group. They showed the levels of dominant follicle and oestradiol in the group that received clomiphene citrate on a daily basis were significantly greater. The group that was given letrozole had an endometrial thickness that was noticeably higher than the group that was given clomiphene citrate. Both the resistance index and the pulsatility index were lower in the group that was given letrozole as well as in pregnant women compared to the group that was given clomiphene citrate and the group that was not pregnant.

DISCUSSION

Polycystic ovarian syndrome (PCOS) is the most common endocrine pathology in females of reproductive worldwide. PCOS is a disease that has more than one cause. The pathophysiology of the disease has been linked to the presence of a number of susceptibility genes, which have been identified. These genes are active in a variety of steroidogenesis and androgenic pathway processes at different degrees. According to the findings of studies on twins, heritability is approximately 70%. The expression of these genes, as well as the genesis and course of the disease, is also significantly influenced by the environment.[16]

Hyperandrogenism and anovulation are complicated. PCOS women generally have increased GnRH pulsatility, which increases pituitary LH secretion and the LH/FSH ratio. FSH aromatizes androgens to estrogen in granulosa cells and matures follicles, while LH promotes theca cell androgen production. Intraovarian androgens promote initial follicle recruitment by stimulating preantral and early antral follicle growth, but they cause atresia in later antral stages. Androgens begin their pro-atretic impact when folliculogenesis changes from the gonadotropin-independent early phase to the FSH-dependent cyclic recruitment phase at 2-5 mm.[17,18]

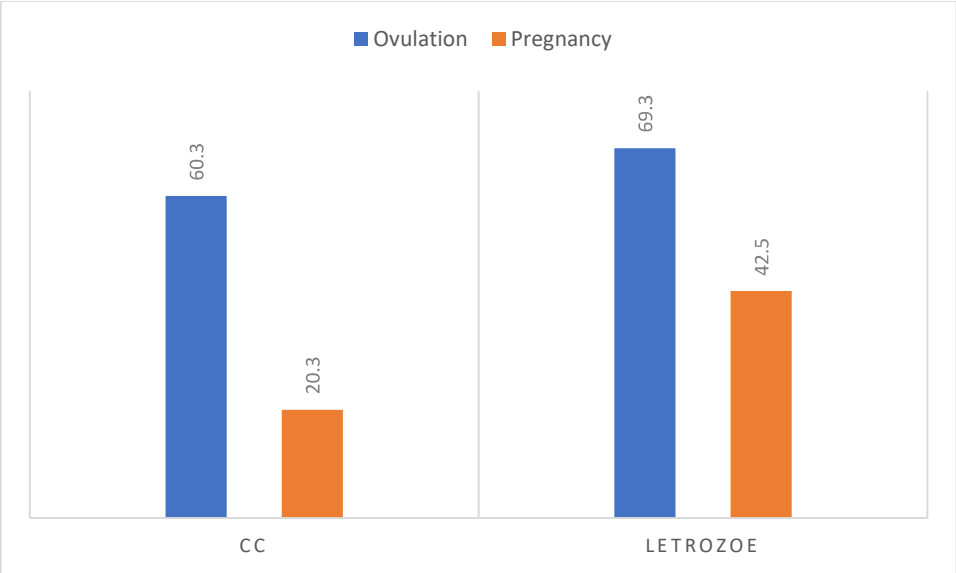

Figure 2. Comparison of ovulation and labor rates of patients receiving CC and LE

In women with PCOS, blood FSH levels are somewhat lower than during the follicular phase, so aromatization of excessive androgens is insufficient and the follicles will not undergo FSH-dependent maturation, resulting in a dominant follicle. In addition, granulosa cells in follicles from anovulatory PCOS patients synthesize AMH at concentrations several

times higher than in ovulatory women and higher than in ovulatory women with polycystic-appearing ovaries, raising the serum AMH level. High AMH levels impede granulosa cell androgen-to-estrogen conversion and follicular maturation because AMH inhibits FSH-driven aromatase complex activity.[18]

The Endocrine Society has no preference for one option over another. The progestin component reduces LH levels, thereby indirectly reducing ovarian androgen production and augmenting sex hormone-binding globulin. In addition, it has been demonstrated that certain progestins possess direct antiandrogenic properties as a direct inhibitor of 5 alpha-reductase activity, preventing the conversion of unbound testosterone to its more potent form, 5 alpha-dihydrotestosterone. Therefore, they are highly effective for treating hyperandrogenism symptoms and regulating the menstrual cycle.

When compared to CC alone, letrozole boosted live birth rates, and the overall level of evidence was moderate. Letrozole's treatment advantages over CC alone were more pronounced in women with greater baseline blood total testosterone levels. There was inadequate evidence of a difference in live birth rates between CC + metformin and CC alone, and the overall certainty of evidence was low, owing to the danger of bias and imprecision. When compared to CC alone, the prospective advantage of CC in conjunction with metformin was more obvious in women with higher baseline blood insulin or HOMA-IR values.[19]

Aromatase inhibitors prevent androgens from converting to estrogens. Low estrogen serum concentrations inhibit negative feedback on the pituitary/hypothalamus and increase pituitary FSH secretion. Letrozole is the most commonly used aromatase inhibitor for ovulation induction; it is administered in a manner similar to that of SERMs, 2.5-5 mg for 5 days after a withdrawal hemorrhage. Letrozole results in an ovulation rate of 70%-84% per cycle and a pregnancy rate of 20%-27%. Due to the brief half-life of letrozole, hot flushes occur infrequently.[20]

Letrozole appears to improve live birth rates and pregnancy rates in infertile women with anovulatory PCOS, compared to selective oestrogen receptor modulator (SERMs), when used for ovulation induction, followed by intercourse.[21] The study was of low scientific quality and has never been published in its entirety in a journal subject to peer review. Subsequent investigations on the use of letrozole for ovulation induction have not demonstrated an increased risk of malformations, despite the fact that none of them have statistical significance. However, prescription of letrozole as an ovulation induction drug has been prohibited in some countries; therefore, patients must be well-informed before receiving treatment with letrozole.[20,22]

CONCLUSION

In comparison to clomiphene citrate, letrozole was related with higher rates of ovulation, pregnancy, and successful delivery of a live baby. Despite the fact that the quality of the data is inconsistent, one study recommends letrozole over clomiphene citrate as an ovulation induction medicine for women who have infertility and PCOS.

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