

The effectiveness comparison between letrozole and clomiphene citrate as ovulation induction therapy in patients of polycystic ovarian syndrome (PCOS)

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ABSTRACT

Letrozole is an aromatase inhibitor that has been tested and proven to be superior to CC in terms of ovulation, pregnancy and birth rates. However, letrozole has the potential to be teratogenic to the fetus. To compare the effectiveness of Letrozole and Clomiphene Citrate as ovulation induction therapy in polycystic ovarian syndrome (PCOS) patients. Methods is Literature review of four databases; PubMed, DOAJ, Cochrane, and Google Scholar published within the last 5 years from 2018-2022. There were 11 studies reporting the effectiveness of Letrozole and Clomiphene Citrate as ovulation induction therapy in polycystic ovarian syndrome (PCOS) patients. Primary and secondary outcomes are used to evaluate outcomes. The key outcomes were the drug's impact on ovulation, birth, pregnancy, multiple pregnancies, miscarriages, and birth defects rates. The effectiveness of combination therapy and monotherapy was also contrasted in this literature study. Based on this literature review, it was found that Letrozole is superior to Clomiphene Citrate as an ovulation induction agent in PCOS patients. Letrozole is also associated with a better probability of pregnancy and birth and a lower chance of multiple pregnancies. The probability of miscarriage and the occurrence of congenital anomalies or defects in the newborn did not differ between the groups receiving letrozole or CC. In addition, the combination of letrozole and CC was superior to letrozole alone in increasing the ovulation rate in women with PCOS. Letrozole is also better and more acceptable than the combination of CC and metformin for inducing ovulation.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder in women, causing infertility because ovulation does not occur in sufferers. PCOS is a disorder that can affect ovarian function so that the

level of luteinising hormone (LH) secretion becomes higher than usual and the secretion of follicle-stimulating hormone (FSH) becomes lower. Increased FSH secretion from the pituitary gland is necessary for follicular growth. High serum LH levels cause an increase in androgen secretion and inhibit FSH induction for LH receptors in the follicles, so that follicles cannot form (Najafi et al., 2020). The main clinical features of PCOS include hyperandrogenism, menstrual disorders, polycystic ovaries, infertility, obesity, hypertension, dyslipidemia, insulin resistance, and type 2 diabetes mellitus. This chronic and heterogeneous endocrine disease affects 5-8% of women of reproductive age (Hu et al., 2018).

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, occurring in 5-10% of women worldwide. PCOS is the most common cause of anovulatory infertility in women, affecting >80% of all cases (Mejia et al., 2019; Park & Chun, 2020; Rezk et al., 2018; Wang et al., 2021; Yan et al., 2022). The prevalence of infertility in women with PCOS varies between 70-80%. Women with anovulatory PCOS who wish to become pregnant are advised to receive ovulation induction therapy (Tsiami et al., 2021).

For several years, Clomiphene Citrate (CC) was recommended as a first-line ovulation induction agent in women with anovulation or PCOS. CC acts as a selective estrogen receptor modulator. This drug works by attaching to the nucleus of the estrogen receptor. As a negative feedback from reduced estrogen secretion, gonadotropin hormone secretion increases, inducing growth of ovarian follicles (Joham & Peña, 2022; Manique & Ferreira, 2022). CC also has an antiestrogenic effect on endometrial development and cervical mucus production, so it has the potential to affect pregnancy even though this drug has effectiveness to increase ovulation (Mejia et al., 2019). Although these drugs can induce ovulation by 60-80%, clinically the pregnancy rate is only 35-40%, attributed to their anti-estrogenic effect on the endometrium. The incidence rate of multiple pregnancies after ovulation induction with CC is around 7-13%, whereas 20-25% of women do not ovulate after administration of CC (Tsiami et al., 2021).

Letrozole belongs to the class of aromatase inhibitors. It was introduced as an ovulation induction agent in 2001. Since then, it has been studied and shown to be superior to CC in terms of ovulation, pregnancy, and birth rates. Nevertheless, its use in clinical practice remains controversial. In Europe, letrozole is not registered for ovulation induction, and its use is prohibited except for approved clinical trials. In addition, letrozole also has potential teratogenic effects on the fetus. In 2005, an abstract presentation reported that the incidence of heart and bone anomalies was higher in infants born after receiving letrozole therapy (Tsiami et al., 2021).

Letrozole works as a highly selective aromatase inhibitor, preventing the conversion of androgens to estrogens. Suppressed estrogen production causes a decrease in negative feedback on the hypothalamus and increases FSH secretion. Another mechanism by which these drugs increase the rate of ovulation is by increasing the sensitivity of the follicles to FSH resulting from a transient increase in intraovarian androgens. Letrozole is superior to CC for ovulation induction because it does not block estrogen receptors in central and peripheral target tissues, and normal central feedback mechanisms remain intact (Mejia et al., 2019). The results showed that Letrozole and Clomiphene Citrate were effective as ovulation induction therapy in Polycystic Ovary Syndrome (PCOS) patients (Keevil, 2019; Nylander et al., 2017). Therefore, we conducted this literature review to compare the effectiveness of Letrozole and Clomiphene Citrate as ovulation induction therapy in *Polycystic Ovarian Syndrome* (PCOS) patients. The background of the study is epidemiological data estimates that polycystic ovarian syndrome / PCOS is experienced by more than 116 million or around 3.4% of women worldwide. PCOS is thought to be the most common metabolic disease experienced by women of childbearing age.

RESEARCH METHOD

The author conducted a search, selection, and review of the literature (Danandjaja, 2014; Sugiyono, 2017, 2018, 2019) using the literature review method regarding the comparison of the effectiveness

of Letrozole and Clomiphene Citrate as ovulation induction therapy in *Polycystic Ovarian Syndrome* (PCOS) patients with the keywords *Letrozole*, *Clomiphene Citrate*, and *Polycystic Ovary Syndrome*. The literature sources used were PubMed, DOAJ, Cochrane, and Google Scholar. From the search results, a total of 71 journals were obtained from Pubmed, 38 DOAJ, 183 Cochrane, and 2,450 Google Scholars. The author chooses literature published within the last 5 years, namely from 2018-2022. After that, a selection of journals with open access criteria was carried out and literature that met the criteria was obtained in 11 journals. Writing begins with reviewing the contents of each literature that meets the author's criteria, brainstorming, and cross-checking with other primary sources.

RESULTS AND DISCUSSIONS

To compare the effectiveness of letrozole therapy with clomiphene citrate (CC), the authors assessed the results based on primary and secondary. The primary results were the rate of ovulation rate, birth rate, pregnancy rate, multiple pregnancy rate, miscarriage rate, and birth defects rate with this drug. In addition, the authors also compared the effectiveness of combination therapy with monotherapy.

The Effectiveness of Letrozole Compared to Clomiphene Citrate Based on the Speed of Ovulation Induction

Research conducted by Tsiami A. showed that infertile patients with PCOS who were treated with letrozole had a higher chance of ovulation compared to those who were given CC. These findings also apply to patients who are given letrozole as the first line of treatment (Tsiami et al., 2021).

Hu S.'s study also showed that letrozole was superior to CC as an ovulation induction agent in PCOS patients who had never received ovulation induction agents before (Hu et al., 2018)

The Effectiveness of Letrozole Compared to Clomiphene Citrate Based on Pregnancy Rate

Research conducted by Tsiami A. also showed the advantages of letrozole compared to CC associated with a higher probability of birth rate. Letrozole is also associated with a better probability of pregnancy and a lower chance of multiple pregnancies. The probability of miscarriage and the occurrence of congenital anomalies or birth defects did not differ between groups receiving Letrozole with CC (Tsiami et al., 2021).

Bansal S.'s study found that compared with CC, treatment of infertile PCOS women with letrozole was more successful in achieving pregnancy (Bansal et al., 2021).

The receptive endometrium (endometrial acceptance) is an important contributor to the success of pregnancy and plays a key role in implanting the embryo. Receptive endometrial growth is under the control of steroid hormones, growth factors and cytokines which are necessary for optimal implantation. Ultrasound is playing an increasingly important role in the evaluation and treatment of infertile patients. Pulsed and color doppler ultrasound used to assess various uterine variables and endometrial/sub-endometrial perfusion, which can ultimately affect endometrial receptivity (Al-Obaidi et al., 2019).

Endometrium receptive during the letrozole implantation window for ovulation induction is superior to CC in PCOS women, which contributes to increased pregnancy rates. Endometrial secretion of FI and avb3 integrin in the uterus during the implantation window could be improved and could be used as non-invasive predictor markers for pregnancy (Wang et al., 2019). Use of CC may be related to endometrial thinning due to prolonged depletion of estrogen receptors in the endometrium (Wang et al., 2021).

Clomiphene citrate significantly downregulates signaling Wnt which can trigger endometrial thinning causing a low probability of pregnancy in women induced by CC due to impaired estrogen signaling (Mehdinejadani et al., 2018).

In PCOS patients, the pattern of molecular expression in the endometrium will be different from that of healthy women. The Wnt pathway, as a regulator plays a key role in tissue homeostasis, and it is this pathway that is disrupted in PCOS patients. In the endometrium, activation of Wnt /b-catenin is modulated by sex hormones to play an important role in cell proliferation, differentiation, motility, survival, embryo implantation, and placental development. signaling Wnt /b-catenin is activated by estrogen and inhibited by progesterone to induce differentiation which is associated with structural and functional changes in the endometrium (Mehdinejadi et al., 2018) .

The Effectiveness of Letrozole Combination with Clomiphene Citrate

The results of a study by Mejia R. showed that the combination of letrozole and CC was superior to letrozole alone in increasing the rate of ovulation in women with infertility and PCOS (Penzias et al., 2020; Saiyed et al., 2016; Witchel et al., 2019; Xi et al., 2015; Xu et al., 2021; Yu et al., 2017). This study found that the combination of letrozole and CC had a higher ovulation rate with an absolute difference of 34% (Mejia et al., 2019) .

The Effectiveness of Clomiphene Citrate Combination with Metformin

Weight loss in PCOS patients who are obese or overweight can improve fertility and reduce the risk of pregnancy complications such as miscarriage, fetal anomalies, development of gestational diabetes mellitus or hypertension. Insulin sensitizing agents, such as metformin, are thought to have beneficial effects in the management of PCOS as suggested by several studies. In conclusion, letrozole is better and more acceptable than the combination of CC and metformin for inducing ovulation in patients with CC-resistant PCOS with higher pregnancy rates (Rezk et al., 2018) .

CONCLUSION

Based on this literature review, it was found that Letrozole is superior to Clomiphene Citrate as an ovulation induction agent in PCOS patients. Letrozole is also associated with a better probability of pregnancy and birth and a lower chance of multiple pregnancies. The probability of miscarriage and the occurrence of congenital anomalies or defects in the newborn did not differ between the groups receiving letrozole with CC. In addition, the combination of letrozole and CC was superior to letrozole alone in increasing the rate of ovulation in women with PCOS. Letrozole is also better and more acceptable than the combination of CC and metformin for inducing ovulation. This research implies that it has become theoretical material for developing theories about PCOS so that it can become a reference for subsequent analysis. Future studies are expected to create the results of this literature review by using quantitative or experimental methods.

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The limitations of this study are that this study only discusses the literature review of the research results of selected journals. Future research can examine in depth using a systematic review or action/experimental research.

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