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Original Research Article

Effect on Ovulation Induction by Letrozole Alone or in Combination with Clomiphene

Vinay Mirajkar
(MD, DGO.)

Associate Professor, Dep. of Obstetrics and Gynaecology, Pacific Institute of Medical Sciences Umarda, Udaipur

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Corresponding author: Dr.Vinay Mirajkar
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Abstract

Introduction: Infertility caused by anovulatory cycles is often due to polycystic ovarian syndrome (PCOS), a hormonal problem that affects people during their reproductive years. PCOS can lead to pregnancy issues, birth defects, and other problems. PCOS is characterized by ovulation disorders, with anovulation and hyperandrogenism having a complex relationship. PCOS can also result in high levels of luteinizing hormone (LH) compared to follicle-stimulating hormone (FSH), which affects follicle development and maturation. Obesity and being overweight are often associated with PCOS. Treatments for infertility include ovarian stimulation and ovulation induction using oral medications such as clomiphene citrate and letrozole.

Aims and Objectives: The intention of this research is to figure out the effect on ovulation induction by letrozole alone or in combination with clomiphene citrate in PCOS.

Methods: The prospective study included infertile couples with women experiencing either oligomenorrhea or normal menstrual periods without ovulation. PCOS criteria were confirmed through high levels of luteinizing hormone, LH to FSH ratio of more than 5, and ultrasound evidence of multicystic ovaries, while prolactin and thyroid hormone levels were normal. Letrozole was given after clomiphene for at least 6 months, and if patients failed to ovulate, a combination of letrozole and clomiphene was administered. Over a three-year period, 70 PCOS patients with resistance to clomiphene and letrozole were treated with 100 mg of clomiphene and 5 mg of letrozole daily for 5 days, timed according to menstrual cycle regularity.

Results: To collect the relevant information the researcher used different kinds of software tools and techniques for experimental analysis. The following tables show patient demographic information. In addition, 70 participants with PCOS participated in the research. The mean age of the patients was between 19 and 37. The average duration of infertility was 4.984.0 years. There were 56 occurrences of primary infertility and 14 occurrences of secondary infertility. Dominant follicles were seen in 20 patients with secondary infertility and 63 cases with primary infertility.

Conclusion: The has concluded that combination of clomiphene citrate and letrozole as a first-line therapy for severe PCOS which would maximize the pharmacotherapeutic effect.

Keywords: PCOS, clomiphene citrate, letrozole, ovulation induction, anovulation.

Introduction

Infertility due to anovulatory cycles is frequently caused by polycystic ovarian syndrome (PCOS). At the present time, polycystic ovary syndrome is a common hormonal problem of people that generally happens during the reproductive years. Due to PCOS problems, it can raise pregnancies issues, birth defects,side effects, and other problems. On the other hand, due to Infertility, ovulation disorders happen, among which polycystic ovarian syndrome (PCOS) is by far the most prevalent. At the same time, it indicates that anovulation and hyperandrogenism have a complicated relationship. Again, Gonadotropin-releasing hormone (GnRH) would be more pulsatile with PCOS, and as a result, it can release pituitary to luteinizing hormone (LH) and also a higher ratio of LH to follicle-stimulating hormone (FSH) [1]. Whereas luteinizing hormone (LH) stimulates theca cells to create androgen, follicle-stimulating hormone (FSH) prompts granulosa cells to convert androgens to oestrogen and mature follicles. Initial follicle development is stimulated by intraovarian androgens at the preantral and early antral stages.

After antral phases, high androgen levels can lead to atresia [2]. On the other hand, the pro-atretic impact of androgens begins whenever folliculogenesis shifts from the gonadotropin-independent stage to the initial phase of FSH-dependent, cyclic recruitment stage at a follicular diameter of between 2 and 5 millimeters. This happens whenever folliculogenesis occurs at a follicular diameter of between 2 and 5 millimeters [3]. Furthermore, this lack of aromatization of outrageous androgens and the follicles' failing to experience the conclusive FSH-dependent maturation, eventually resulting in a a prevalent follicle, blood FSH statuses in females with PCOS are relatively insufficient during the follicular phase [4]. Again, ovulation basically arises when a grown egg is released from an ovary. At the same time, the reason for a grown egg to be released from an ovary is due to fertilization by male sperm. Even , this egg is not fertilized, it can be sent out of the body during people's periods. Alongside, granulosa cells in anovulatory PCOS patients' follicles synthesis AMH at levels several times greater than those of ovulatory women and higher compared to those of ovulatory women with polycystic-appearing ovaries; as a consequence, the blood level of AMH is higher in PCOS patients.

High amounts of AMH will prevent granulosa cell change of androgens to oestrogens and negatively impact ultimate follicular maturation because AMH inhibits the FSH-driven aromatase complex activity [5]. Hence, there are a lot of little antral follicles in women with PCOS. Obesity and being overweight are frequently linked to polycystic ovary syndrome. Obesity may lead to compensatory hyperinsulinemia and insulin resistance, both of which will increase hyperandrogenism by promoting the production of androgen by theca cells[6]. On the other hand, the primary purpose of this conventional therapies are related with PCOS anovulatory and this infertility shift the ratio of intraovarian steroid synthesis away from an excessive androgen synthesis caused by LH-insulin-leptin that effects in follicular atresia and towards an FSH-driven conclusive growth of a a prevalent follicle.

Normally, ovulation comes 14 days before the beginning of menstruation. Whenever the menstrual history is hazy or inconclusive, a postovulatory serum progesterone level obtained during the expected mid-luteal phase might confirm ovulation. Polycystic ovarian syndrome (PCOS), which impacts 70% percent women with anovulation, is the most usual cause of the problem. Apart from PCOS, obesity has been associated to anovulation; women with a body mass index above 27

are more vulnerable to anovulatory infertility than women with a BMI in the normal range. [7]

Idiopathic chronic anovulation (7-8%), functional hypothalamic amenorrhea (7-8%), elevated androgens from adrenal hyperplasia or tumours (2%), thyroid disease (2%-3%), pituitary disease (e.g., prolactinoma, 13%), elevated androgens from pituitary disease (e.g., 2%), androgen hyperplasia (2%), are some of the other causes. Women with eating disorders are more likely to experience ovulation problems due to anovulatory ovulation. Treatments for infertility include ovarian stimulation, in which several immature follicles are intentionally stimulated to develop into mature ones, and ovulation induction, in which therapeutic measures are employed to bring about ovulation. [8]

Two oral treatments are used for ovulation induction. By blocking the adverse feedback result of mixing estradiol, the selective oestrogen receptor modifier clomiphene citrate increases the frequency of pituitary gonadotropin-releasing hormone (FSH) and luteinizing hormone (LH) synthesis, which in turn stimulates the development of ovarian follicles. Letrozole inhibits aromatase, which lowers serum levels of estradiol and increases pituitary gonadotropin production. Less than 10% of pregnancies result in multiples with clomiphene citrate and aromatase inhibitors, with twin pregnancies accounting for the bulk [9]. According to the Pregnancy in Polycystic Ovary, letrozole is the first-line medication for PCOS patients who are having ovulation induction. Some oral medications are less effective in treating hypogonadotropic hypogonadism in women because their endogenous pituitary gonadotropin response may be minimal or absent.

The physiological elevation of natural FSH and LH is restored when pulsatile GnRH injection is administered to these individuals. This allows for the induction of follicular maturation and ovulation, which are both necessary steps. Altering the pulse frequency helps simulate the biological fluctuation that occurs in the variability of the GnRH pulse. There have been no cases of severe ovarian hyperstimulation syndrome described, and pregnancy rates after up to six months of treatment with pulsatile GnRH range from 93 to 100 percent [10]. There is also the option of using exogenous gonadotropins in order to directly stimulate the ovarian follicles. When a woman suffers from hypogonadotropic hypogonadism, she must need an exogenous ovulatory trigger in order to overcome her intrinsic inability to ovulate.

To stimulate the eggs in a way analogous to ovarian stimulation, physicians can use clomiphene citrate, aromatase inhibitors, gonadotropins, or a combination of these drugs. In order to treat unexplained infertility, ovarian stimulation is paired with intrauterine insemination; live birth speeds depend on the diagnosis, sperm viability, and ovarian response. Furthermore, another severe side impact of gonadotropin use is ovarian hyperstimulation syndrome (1%–5% of cycles), which can result in ascites, electrolyte imbalance, and hypercoagulability. Therefore, the regime of gonadotropin treatment can be accomplished under the path of a reproductive endocrinologist.

Materials and methods

Study design

This is a prospective study conducted during the period of one year on 70 patients with anovulatory PCOS who visited the outpatient department in our hospital for treatment of infertility. Either oligomenorrhea or normal menstrual periods without ovulation were experienced by the women in these relationships (Levels of progesterone on day 21 of respective cycles were used to determine anovulation). Additional PCOS criteria found in such

patients included high levels of luteinizing hormone, an luteinizing hormone to FSH ratio of more than 5, with ultrasound evidence of multicystic ovaries. Nevertheless, prolactin as well as the hormone which activates the thyroid were both within normal ranges. The only cause of each patient's sterility was ovulatory dysfunction, despite all of their hysterosalpingograms and spermogramme being normal. These patients were placed on letrozole after taking clomiphene for at least 6 months because they could not develop dominant follicles. Letrozole was given four times to them. After that, patients who failed to ovulate were given letrozole and clomiphene in combination treatment. This happened with 32 patients. Throughout a three-year period, 70 PCOS patients having clomiphene & letrozole resistance were accepted into the study. The cases received 100 mg of clomiphene and 5 mg of letrozole daily for 5 days. Those with regular menses received the medication after the second or third day of the menstrual cycle, while those with oligomenorrhea received it after progesterone-induced bleeding.

Inclusion and exclusion criteria

Included are patients who visited our hospital's outpatient clinic, adhere to the study protocol, and offer their informed consent. Those who consent to participate in the study voluntarily do so. 80 patients in total were involved in the trial.

The study did not provide the patients who weren't faithful to the study protocol, did not complete it, or did not give their consent.

Statistical analysis

The study used SPSS 25 software for effective statistical analysis. The continuous data was expressed as mean ± standard deviation while discrete data was expressed as frequency and its respective percentage.The proper percentage comparisons between the various groups were made using the mean values, standard deviations. The study employed ANOVA as the main statistical tool for analysis. Level of significance was considered to be $P < 0.05$.

Ethical approval

The authors gave the patients a proper justification of the study. The patients' consent has been obtained. The study's methodology has indeed been approved either by hospital's ethical review board.

Results

The patient demographics are displayed in Table 1 below. In the trial, 70 PCOS individuals were enrolled. The age of the average patient was 29.02±7.9 (between 19 and 37). Infertility lasted an average of 4.98±4.0 years. 56 cases of primary infertility and 14 cases of secondary infertility were observed. Twenty patients with secondary infertility and 63 patients with main infertility both developed dominant follicles. In terms of menstrual periods, 12 patients had regular cycles, 3 patients had menometrorrhagia, and 56 patients had oligomenorrhea. A total of 32 individuals had hirsutism, and their mean BMI was 28.1±3.7. 17 individuals had a history of miscarriages. Luteinizing hormone levels averaged 10.25±4.67 mIU/mL, FSH levels averaged 5.35±2.1 mIU/mL, and thyroid-stimulating hormone levels averaged 1.89±1.1 mIU/mL on day 3 of the cycle.

Table 1: Baseline characteristics of the study sample

Characteristics	Value
Mean age of patients, years	29.02 ± 7.9
Fertility duration	4.98 ± 4.0
Menometrorrhagia	3 (4.2%)
Oligomenorrhea	56 (80%)
Regular menstruation	12 (17.1%)

History of previous miscarriage	17 (24.3%)
Hirsutism	32 (45.7%)
Mean body mass index	28.1 ± 3.7
Third day of menstruation mean LH	10.25 ± 4.67 mIU/mL
Mean TSH	1.89 ± 1.1 mIU/mL
Mean FSH on the third day of the period	5.35 ± 2.1 mIU/mL
Mean estradiol on 3rd day of menstruation	91.11 ± 22 pg/mL

Table 2 presents the outcome of treatment in two groups of individuals: those treated with Letrozole alone (n = 38) and those treated with a combination of Letrozole and synthetic human follicle-stimulating hormone (FSH) (n = 32). The table includes various outcomes and measures related to fertility treatment, along with their corresponding values for each treatment group.The table shows that 18 out of 38 patients (47.36%) in the Letrozole alone group had their dominant follicle visualized under transabdominal sonography (TAS), while in the combination group, 22 out of 32 patients (68.75%) had their dominant follicle visualized under TAS. The p-value of 0.0358 indicates a statistically significant difference between the two groups, suggesting that the combination treatment may result in a higher rate of dominant follicle visualization compared to Letrozole alone. The table presents the average endometrial circumference in millimeters. The Letrozole alone group had an average endometrial circumference of 8.34 ± 1.8 mm, while the combination group had an average endometrial circumference of 8.66 ± 1.2 mm. The p-value of 0.0669 indicates that the difference in average endometrial circumference between the two groups is not statistically significant. The table shows that the Letrozole alone group had an average quantity of synthetic human FSH utilized in treatments of 4.1 ± 1.1, while the combination group had an average quantity of 3.9 ± 1.25. The p-value of 0.057 suggests that the difference in the quantity of synthetic human FSH utilized between the two groups is not statistically significant. The table indicates that 8 out of 38 patients (21.05%) in the Letrozole alone group experienced a miscarriage, while 3 out of 32 patients (7.89%) in the combination group experienced a miscarriage. The p-value of 0.047 suggests a statistically significant difference in the occurrence of miscarriage between the two groups, with a lower rate of miscarriage in the combination group compared to Letrozole alone. The table presents the average number of dominant follicles in each treatment group. The Letrozole alone group had an average of 2.7 ± 1.5 dominant follicles, while the combination group had an average of 3.1 ± 1.4 dominant follicles. The p-value of 0.0483 suggests a statistically significant difference in the number of dominant follicles between the two groups, with a higher number of dominant follicles in the combination group compared to Letrozole alone. The table indicates the number of patients who had twin fetuses and single fetuses in each treatment group, but it does not provide p-values or additional information for interpretation. Overall, the table suggests that the combination of Letrozole and synthetic human FSH may result in higher rates of dominant follicle visualization, lower rates of miscarriage, and a higher number of dominant follicles compared to Letrozole alone in the context of fertility treatment. However, there were no statistically significant differences observed between the two groups in terms of average endometrial circumference and quantity of synthetic human FSH utilized. It's important to interpret the results in the context of the specific study and consult with a medical professional for a comprehensive understanding of the findings.

Table 2: Outcome of treatment in Individuals

Outcome	Patients with Letrozole alone n = 38	Patients with Combination n = 32	p-value*
Patients whose dominant follicle visualized under TAS	18 (47.36)	22 (68.75)	0.0358
Average Endometrial Circumference (mm)	8.34 ± 1.8	8.66 ± 1.2	0.0669
Treatments utilizing synthetic human follicle-stimulating hormone quantity	4.1 ± 1.1	3.9 ± 1.25	0.057
Miscarriaige occurred	8 (21.05)	3 (7.89)	0.047
Number of Dominant Follicles	2.7 ± 1.5	3.1 ± 1.4	0.0483
Twin fetus	10 (26.31)	5 (13.15)	
Single fetus	28 (73.68)	27 (71.05)	

***Level of significance P < 0.05; TAS, Trans-Abdominal Sonography**

Discussion

Third-generation selective aromatase inhibitor letrozole prevents androstenedione and testosterone substrates from converting into oestrogen. It is a medication that is frequently suggested for the therapy of postmenopausal breast cancer, and it just indicated its effectiveness as a representative for ovulation induction [11]. Compared to CC, letrozole offers a number of clear advantages. Both oestrogen agonistic and antagonistic effects are provided by clomiphene. The hypothalamic oestrogen receptors are depleted by CC, which increases GnRH secretion, pituitary gonadotropin release, and ovarian movement [12]. Although it is an appealing therapy due to the high ovulation rate (60–90%), the pregnancy rate of 10–20% [13] is unsatisfactory. Inadequate pregnancy accelerations with CC have been attributed to either its interference with the corpus luteum's ability to function or its peripheral anti-estrogenic activities, which mostly involve the endometrium and cervical mucus [14]. When clomiphene fails, gonadotropins have been employed, but they are expensive, can cause hyperstimulation, and require strict supervision and monitoring. Letrozole has pregnancy results that are comparable to those of gonadotropin, but it is less expensive and does not have the side effects of gonadotropin [14,15].

Letrozole use for ovulation induction has drawn criticism since it may disrupt tissues' normal aromatase function during the early stages of embryonic development and may even be teratogenic. Since the late 1990s, letrozole is used for ovarian stimulation.

On the other hand, it is an efficient oral agent for this objective, according to analyses. When carried in the premature follicular stage to cause ovulation, it does not significantly involve metabolites, a half-life of about 30-60 hours, and can be totally destroyed from the body by the period of origin embedding.Letrozole may raise the incidence of bone and heart abnormalities in babies, according to Biljan et al. (2005) research [16].

When drawing a parallel between the CC group (2.6%) or spontaneous conception (3.2%), Forman et al. set up that the letrozole group had a lower malformation rate (0.0%) [17]. In a randomized research by Badawy et al, writers noted a comparable malformation velocity in each group after linking 129 deliveries in each of the letrozole, spontaneous pregnancy, and CC groups. Furthermore, in this letrozole group are registered one incidence of a complete cleft palate, one patient of a severe congenital heart deficiency, and two

patients of talipes equinovarus in the CC and spontaneous pregnancy group. In our investigation, the CC group had three cases of hypospadias, two of which were of the severe (penoscrotal) form. [18]

Meijer et al. discovered a strong correlation between using clomiphene and having severe hypospadias (OR = 6.08) [19]. In contrast, Sorenson et al study found no evidence that taking clomiphene affected the chance of hypospadias [20]. After removing twin pregnancies, Forman et al. showed reduced birth significance in the CC group described in relation to the letrozole group [17].

Although letrozole, CC, and spontaneous pregnancies differed in terms of birth weight, other researchers did not find this to be the case [21]. Letrozole is well known to reduce the likelihood of multiple pregnancies due to mono follicular development. Although the distinction was not statistically important, we also glimpsed that the CC group retained a higher balance of twins than the letrozole group.

An increase in heart abnormalities was observed in the pregnancies following CC, as per a people-oriented multicenter case that can control analysis of intense birth defects [22]. Furthermore, Letrozole appears to be at least as adequate as CC for causing ovulation and live birth in a review article by Casper et al, with some probable benefits over CC [23]. The National Institute of Child Health and Human Development (NICHD) and Reproductive Medicine Network is completing ongoing, sizable randomized multicenter examinations that can potentially be offered definitive evidence of the effectiveness and protection of Letrozole compared with CC for the therapy of infertility [24]. Tamoxifen and letrozole have been shown to have success rates for ovulation and pregnancy that are equivalent to those of CC in studies. This result was published in a network meta-analysis comparing a number of various treatments for anovulatory infertility was published [25]. CC has been the go-to drug for ovulation induction since the 1960s. Network meta-analyses compare various therapeutic methods' effectiveness [26].

Therapy with letrozole or SERM + metformin produced equivalent live birth rates compared to gonadotropin stimulation, and the danger of multiple pregnancies was minimal. Letrozole treatment led to increased ovulation, pregnancy, and live birth rates with a reduced multiple birth rate when compared to ovulation induction with CC alone.

Therapy with metformin alone or in conjunction with CC was no more effective than CC alone in the RT, despite the fact that earlier nonrandomized studies revealed significant ovulatory rates on the medicine in PCOS. Letrozole, an aromatase inhibitor with such a slightly distinct mechanism of action, is being investigated as a substitute to clomiphene due to its high rate of side effects, low success rate (only 78% of pregnancies end in a live birth after 6 cycles), and high risk of multiple births (between 3 and 8 %). As mono follicular recruitment is linked with a lower many pregnancy rates, it was expected that letrozole would improve pregnancy outcomes.

An RT of letrozole or CC was conducted to evaluate the notion that letrozole might be more effective than clomiphene in producing normal birth as well as comparable effectiveness and safety [27]. During letrozole therapy in contrast to CC, average ovulation rates (62% vs. 48%) and live birth rates (28% vs. 19%) were considerably higher. In spite of the fact that the twin gestation rate was less with letrozole than it is with CC (3.4% vs. 7.4%), the trial lacked the ability to identify a significant difference in this endpoint birthrate.

Although letrozole has become the standard treatment for PCOS women

seeking to induce ovulation [28], there is still a high prevalence of nonresponse. Mejia et al. suggested an unique regimen that combines clomiphene and letrozole in an effort to effectively enhance PCOS women's capacity to induce ovulation. To test the hypothesis that the synergistic effects of letrozole, an aromatase inhibitor, and CC, a selective oestrogen receptor modulator, would result in a higher ovulation rate with combination therapy than letrozole alone. Mejia et al. evolved a pilot RT of letrozole or a mix of letrozole and CC [29]. Considering letrozole alone to combination therapy after a single treatment, the likelihood of ovulation increased considerably. [30]

Conclusion

The study has concluded that patients resistant to single therapy of clomiphene citrate or letrozole, can be given with combined therapy of clomiphene citrate and letrozole, for successful ovulation induction. The combination can be advised as the first line therapy for ovulation induction in severe PCOS which can be cost effective as well. The authors suggest to conduct more similar studies in different PCOS cases which can bring more varied conclusion. To better understand how the medicine combination works on a larger patient population, more studies should be conducted in individuals with other chronic conditions.This present study would contribute in the management of infertility and ovulation induction in anovulatory individuals.

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