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Original Article

Ovulation induction in women with polycystic ovarian syndrome: Clomiphene citrate or letrozole?

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Abstract

Objective

The objective of this study was to determine first-line infertility therapy in polycystic ovarian syndrome (PCOS) and to compare between clomiphene citrate (CC) and aromatase inhibitors (letrozole) as the standard treatment.

Patients and methods

This is a prospective randomized study. The study was conducted at El-Galaa Assisted Reproduction Unit, El-Galaa Maternity Teaching Hospital, Cairo, Egypt. Eighty-eight women with PCOS were randomized into two groups. Rotterdam criteria were used to define PCOS: oligomenorrhea less than or equal to 8 menses/year plus either PCOS on ultrasound or clinical/biochemical hyperandrogenism, with the exclusion of other causes. Forty-four patients were randomized to the letrozole group (82 cycles), and the other 44 were randomized to the CC group (78 cycles). The aromatase inhibitor letrozole (5 mg/day) and CC (100 mg/day) were administered orally on days 3–7 of menses.

Results

Number of follicles, endometrial thickness, estradiol levels on human chorionic gonadotropin day, and pregnancy rates were measured in both groups. The mean age, parity, and duration of infertility in both groups were similar. The number of follicles sized more than 15 mm in diameter was statistically significantly higher in the CC group (3.4 ± 0.4 vs. 2.03 ± 0.2). Ovulation occurred in 68.2% (56/82) of letrozole cycles and 74.3% (58/78) of CC cycles without a statistically significant difference. Median serum estradiol concentrations were significantly higher in the CC group than in the letrozole group (396 ± 84.4 vs. 266.2 ± 55.1 pg/ml). Endometrial thickness by transvaginal ultrasound at the time of human chorionic gonadotropin administration was not statistically significantly different in the two groups (7.8 ± 2.2 and 8.1 ± 1.2 mm in letrozole and CC groups, respectively). The pregnancy rate per cycle was 9.7% in the letrozole group and 7.6% in the CC group without significant statistical difference between the groups.

Conclusion

Both letrozole and CC have comparable results, with no specific advantage of one over the other for ovulation induction in women with PCOS.

Keywords: Clomiphene citrate, letrozole, pcos, pregnancy

Introduction

Anovulation is responsible for ~20% of female infertility, of which polycystic ovary syndrome (PCOS) is a significant cause [1]. It has been estimated that 55–75% of patients with PCOS are infertile owing to long-term anovulation [2–4].

Clomiphene citrate (CC) is frequently used for ovulation induction and is highly effective in initiating ovulation in patients with PCOS [2]. Although the use of CC results in a 60–85% ovulation rate, the pregnancy rate is only 10–20% per cycle [5–8]. This discrepancy between the ovulation and pregnancy rates could be attributed to clomiphene resistance, which refers to the persistence of anovulation after standard CC therapy, which occurs in 15–20% of patients [9]. Moreover, CC may hurt the cervical mucus and the endometrium.

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Aromatase inhibitors (letrozole) originally were developed for the treatment of breast cancer. Letrozole is a specific, reversible, nonsteroidal aromatase inhibitor that suppresses estrogen biosynthesis [10]. It has been suggested that letrozole increases endogenous gonadotropin secretion, as seen with CC. However, unlike CC, letrozole does not cause a decrease in estrogen receptors [11].

This study aims to compare the result of using CC and letrozole for ovulation induction in patients with PCOS.

Patients and methods

Eighty-eight patients with a diagnosis of PCOS were randomized into two equal groups. We used Rotterdam criteria to define patients with PCOS. The first group received letrozole (5 mg/day, Femara; Novartis Pharma AG, Basel, Switzerland). The second group received CC (100 mg/day) (Hoechst Marion Roussel Inc., Cairo, Egypt). Both treatments were administered on days 3–7 of the menstrual cycle.

All women were recruited from El-Galaa Assisted Conception Unit, El-Galaa Maternity Teaching Hospital, Cairo, Egypt, between the period of August 2015 and September 2016. Hospital ethical approval has been obtained.

All women had patent fallopian tubes proved by hysterosalpingography. Their male partners had normal semen analysis parameters according to the modified criteria of the WHO. All patients were monitored by transvaginal ultrasound for the mean follicular volume and thickness of the endometrium on the days 10, 12, and 14 of the cycle. Serum estradiol (E2, pg/ml) concentration was measured at the time of human chorionic gonadotropin (hCG) injection. The hCG injection (5000 IU, intramuscular) was given when the leading follicle measured more than 18 mm in diameter. Intercourse was advised to be performed 24–36 h after the hCG injection. The serum hCG concentration was determined 2 weeks after the hCG injection in the absence of menstruation for diagnosis of pregnancy.

Results

Eighty-eight patients participated in the study (160 cycles). All patients were scheduled for timed intercourse. There were no statistically significant differences between the two groups in age, duration of infertility, BMI, and baseline follicle-stimulating hormone and luteinizing hormone. The number of follicles more than 18 mm was statistically significantly higher in the CC group (Tables 1 and 2). Endometrial thickness, by transvaginal ultrasound, at the time of hCG administration was not statistically significantly different in the two groups (7.8 ± 2.2 and 8.1 ± 1.2 mm in the letrozole and CC, respectively). The time needed to achieve a dominant follicle was statistically significantly longer in the letrozole group (12.5 ± 1.20 vs. 9 ± 1.8 days). Serum E2 concentrations were statistically significantly higher in the CC group. Ovulation occurred in 56 (68.2%) of 82 cycles in letrozole group and 58 (74.3%) of 78 cycles in the CC group, without a statistically significant difference between the two groups. Pregnancy occurred in eight (9.7%) of 82 cycles in the CC group and six (7.6%) of 78 cycles in the letrozole group; the difference was not statistically significant. There were neither miscarriages nor multiple pregnancies in either group.

Discussion

For anovulatory patients with PCOS, ovulation induction is an essential treatment for them. It considered as the most common endocrine disorder in women with PCOS, with a prevalence of 6–10% based on the National Institute of Health Criteria, and as high as 15% when the broader Rotterdam criteria are applied [12]. Regarding infertility, ovulatory dysfunction is one of the significant causes, affecting 25–30% of infertile couples. There is an increased incidence of WHO Group II Anovulatory Infertility in women with PCOS. In the UK, studies reported a prevalence of oligoanovulation/anovulation of between 60 and 80% among women with PCOS using the preexisting European diagnostic criteria [13–15]. Treatment with ovulation-induction medications for many of these women will be required to achieve pregnancy.

CC is the most commonly prescribed medication for ovulation induction when women are anovulatory. Despite the high rate of ovulation by CC, pregnancy rates per cycle remain relatively low. This could be attributed to the antiestrogenic effect of CC, producing cervical mucus thickening and thinning of the endometrium [16–18]. Inappropriate development of the endometrium is associated with low implantation rate and early pregnancy loss owing to luteal phase defect [16,19]. Overall, 20–25% of patients do not respond to CC despite high doses. Because the antiestrogenic effect is dose dependent, a daily dose of CC more than 150 mg is not recommended and it can be considered a high dose.

Letrozole, an aromatase inhibitor, is widely used and is US Food and Drug Administration approved for the indication of the treatment of hormonally responsive breast cancers in a postmenopausal woman. Letrozole is an aromatase inhibitor that is thought to promote follicle-stimulating hormone release from the hypothalamic–pituitary axis in response to decreased estrogen feedback from the decreased peripheral conversion of elevated circulating androgens, especially in women with

Table 1: Characteristics of the patients

	Letrozole	CC	*P*
Number of patients	44	44	
Number of cycles performed	2 (1-3)	2 (1-3)	0.56
Age	31.1±2.8	32.5±3.8	0.8
Duration of infertility (years)	4 (1-10)	5 (1-9)	0.06
BMI (kg/m^2)	32.1±3.4	34.2±3.2	0.69
FSH (IU/ml)	5.2±2.8	5.8±2.3	0.74
LH (IU/ml)	10.5±1.6	12.1±2.4	0.81

Data are given either as mean±SD or as median (range). CC, clomiphene citrate; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Table 2: Outcome in letrozole and clomiphene citrate groups

	Letrozole (n=82 cycles) (mean±SD)	CC (n=78 cycles) (mean±SD)	*P*
Number of follicles >18 mm in diameter on the day of hCG	2.03±0.2	3.4±0.4	<0.006 (S)
Endometrial thickness on the day of hCG (mm)	7.8±2.2	8.1±1.2	NS
E2 on the day of hCG (pg/ml)	268±72	390±80	0.028 (S)
Duration of stimulation (days)	12.5±1.20	9±1.8	0.029 (S)
Ovulation rate [*n* (%)]	56/82 (68.2)	58/78 (74.3)	NS
Pregnancy rate per cycle [*n* (%)]	8/82 (9.7)	6/78 (7.6)	NS
Twin rate [*n* (%)]	0/8 (0)	0/6 (0)	NS

CC, clomiphene citrate; E2, estradiol; hCG, human chorionic gonadotropin; S, significant. $P<0.05$, statistically significant difference.

PCOS. The use of letrozole, an aromatase inhibitor, instead of CC, for ovulation induction was introduced more than 10 years ago [20]. Mitwally and Casper [21] demonstrated that letrozole resulted in ovulation induction in CC failures as well as led to augmentation of ovulation in women with thin endometrium owing to CC use.

The pregnancy in PCOS, now known as pregnancy in PCOS I, is the most significant randomized controlled trial for pregnancy rate with metformin alone, CC alone, or CC and metformin. Pregnancy in PCOS I has shown a 49% ovulation rate during 6 months, an overall 23% live birth rate, a 3–4% chance of twins, and a 2% incidence of triplets [22]. Another study has reported ovulation rates of 70–80% on CC, but with actual pregnancy rates of only 30–40% [23]. Numerous studies in patients with anovulatory PCOS using letrozole versus CC have demonstrated ovulation rates with letrozole from 61–81%, with conception rates with letrozole between 10 and 40% in women with PCOS, and lower multiple rates [24–26].

In 2005, at the American Society for Reproductive Medicine meeting, an abstract from a Canadian group compared 150 letrozole cycle-conceived babies with 36 050 spontaneous conceptions. These Canadian groups reported that there was no significant difference in the overall incidence of congenital malformations, but there were increased cardiac and locomotor abnormalities [27].

On 17 November 2005, Novartis mailed a letter to all physicians advising that Femara was contraindicated in women with premenopausal endocrine status, in pregnancy, and/or lactation owing to the potential for fetal malformations. The warning sent by Novartis was issued globally to healthcare professionals. Health Canada and the Food and Drug Administration echoed these warnings.

In response to the earlier study, a 2006 Canadian multicenter study [28] compared birth outcomes in women conceiving after use of CC or letrozole. The study included 911 babies during 5 years and found that overall congenital malformations and chromosomal abnormalities were 2.4% in the letrozole group and 4.8% in the CC group. Tulandi *et al.*[28] concluded that there was no overall difference in the rates of major and minor malformations, but it appeared that congenital cardiac anomalies were less frequent in the letrozole group. No other published articles have supported the increased risk of congenital birth defects with the use of letrozole for ovulation induction [20].

In March 2012, the European Medicines Agency completed a review of 'Femara'. No therapeutic indication was listed for ovulation induction, and it did not recommend use of Femara in premenopausal women, owing to the potential for adverse effects on the embryo or fetus [29].

Malloch *et al.*[30] published a 13-question survey to assess the clinical use and practice attitudes among Society for Assisted Reproductive Technology members regarding the use of letrozole for ovulation induction and infertility treatment. The survey concludes that most of the physicians surveyed use letrozole for ovulation induction despite the current US Food and Drug Administration warning. Even when accounting for non-respondents, more than 25% of physicians indicated success with letrozole use. Questions regarding doses and clinical concerns about letrozole revealed no standardized manner of letrozole administration despite broad interest; therefore, additional research is warranted.

In this study, letrozole was compared with CC as a first-line therapeutic agent for ovulation induction in patients with PCOS. The number of follicles more than 18 mm in diameter on the day of hCG and the E2 level were significantly higher in the CC group. However, despite this significant difference, the pregnancy rates of the two groups were comparable.

Regarding the endometrial thickness, it was slightly thicker in the CC group but not statistically significant. The endometrial thickness may be owing to more growing follicles and the higher levels of estrogen in the CC group. The endometrial thickness was significantly higher with CC compared with the letrozole group in a study by Badawy *et al.* [26] (9.2 ± 0.7 vs. 8.1 ± 0.2 mm) and in a study by Rodriguez-Purata *et al.* [31] (8 ± 2.4 vs. 7.6 ± 2.4 mm). Begum *et al.* [25] showed a significantly higher endometrial thickness with the letrozole group (10.37 ± 1.2 vs. 9.03 ± 0.89 mm). Cortinez *et al.* [32] found typical morphologic features of the endometrium with the full expression of pinopodes during the implantation window when letrozole was used. On the contrary, no significant difference has been noted by other studies regarding the effect of either drug on the endometrium [33-35].

Currently, it is unknown whether letrozole or CC is more efficient for ovulation induction in patients with PCOS.

The pregnancy in PCOS II trial, currently in progress from the National Institute of Child Health and Human Development-Reproductive Medicine Network, will enroll 750 patients randomized to CC or letrozole, to answer the question of live birth rate and multiple rates with CC versus letrozole use in this population [35].

Conclusion

This study showed that letrozole is as effective as CC in patients with PCOS who previously have not been treated with other ovulation-induction agents.

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Conflicts of interest

There are no conflicts of interest.

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