

Clinical Observation of 242 Cases of Polycystic Ovary Syndrome

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Abstract

Objective: To compare the clinical effect and safety between letrozole (LE) and clomiphene citrate (CC) stimulated cycles in women with polycystic ovary syndrome (PCOS). To evaluate the effectivenesses and benefits of letrozole for ovulation induction in infertile women with PCOS. **Methods:** We retrospectively analyze the clinical data of 242 cases of the first ovulation induction cycle patients with PCOS, who referred to the Department of Reproductive Medicine, The First Affiliated Hospital of Yangtze University from June 2016 to June 2018, and were randomly divided into letrozole group and control group. The experimental group received Letrozole 2.5 mg/d for 5 days during days 3 - 7 of menstrual cycle. The control group was given clomiphene citrate 100 mg/d for 5 days during days 3 - 7 of menstrual cycle. Progynova will be used when the follicular diameter is 14 mm. **Results:** Letrozole group had less mature follicles, lower estrogen levels, thicker endometrium and higher ovulation rate in HCG day. But there is no difference between two groups in clinical pregnancy rate, single pregnancy rate, abortion rate, prenatal pregnancy delivery and newborns. **Conclusion:** Letrozole and clomiphene citrate have similar effect on ovulation induction, but we still need a lot of clinical data of letrozole about the safety of follicle, embryo, fetus and newborns.

Keywords

Polycystic Ovary Syndrome, Clinical Pregnancy Rate, Letrozole, Clomiphene Citrate

1. Introduction

Polycystic ovary syndrome (PCOS) is caused by a variety of factors. Non-ovulation

or rare ovulation is one of the main reasons for infertility. Although the etiology of PCOS has not been completely clarified, there have been many years of historical experience in the induction of ovulation therapy for PCOS. Clomiphene citrate (CC) is the first-line ovulation-promoting drug recommended by the World Health Organization (WHO). However, during the clinical observation process, CC resistance was found in many patients, affecting cervical mucus, and affecting the side effects of submucosal intima, thereby affecting pregnancy outcomes. Letrozole (LE) is a third-generation selective non-steroidal aromatase inhibitor that induces ovulation by inhibiting estrogen production. The ovulation effect and safety of LE are in the end.

According to a recent review, letrozole appears to improve live-birth and pregnancy rates in anovulatory women with PCOS, compared to CC. Letrozole is not associated with any anti-estrogenic effects on endometrium. This is supported by studies reporting adequate endometrial thickness during letrozole treatment [1].

In this study, 242 cases of ovulation-promoting patients treated with ovulation therapy were prospectively controlled to explore the clinical application of LE.

2. Materials and Methods

2.1. Research Object

242 cases of PCOS patients from July 2016 to June 2018 in the work were collected. We performed the first cycle of ovulation in this center, randomly divided into LE group and CC group.

Inclusion criteria: PCOS diagnostic criteria according to Rotterdam criteria (ovulation thinning or anovulation, ovarian polycystic changes and hyperandrogenic laboratory tests or clinical manifestations, ruled out other cases), age 20 - 33 years, luteinizing hormone 3 - 12 mmol/L, normal prolactin, at least one side of tubal patency (hysterosalpingography/peritoneal laparoscopy), normal uterine cavity imaging (uterine hysterosalpingography/color ultrasound/hysteroscopy), normal semen (fifth version of semen standard) And normal sexual life.

Exclusion criteria: Bilateral hydrosalpinx, tuberculosis, ovarian endometriosis, ovarian cyst, adenomyosis, endometrial polyps, intrauterine adhesions, history of uterine and ovarian surgery, and other factors that have been found to affect pregnancy.

2.2. Treatment Program

LE group menstrual 3 - 7 days to give 2.5 mg orally, began to monitor follicular growth after discontinuation, when the follicle diameter reached 14 mm plus progynova 1 mg/day until the follicle mature (18 - 20 mm), injection HCG10000u. Guide the same room and give support to the corpus luteum after ovulation. The CC group received oral administration of 100 mg on the 3rd to 7th days of menstrual period. The other processes of monitoring were the same as above.

2.3. Monitoring Indicators

Follicle monitoring was performed after discontinuation of the patient. The diameter of the dominant follicles was less than 14 mm. Monitoring was performed every 2 to 3 days. When the diameter of the dominant follicles was greater than 14 mm, daily monitoring was performed and urine LH strips were combined until the dominant follicle diameter was greater than 18 mm, injection of HCG. Monitoring of the patient's endometrium thickness, number of mature follicles, HCG injection on the day of the female two peak level, ovulation rate, clinical pregnancy rate, early pregnancy abortion rate. When more than three dominant follicles are mature, it is recommended that the patient cancel the cycle. Gonadotropin should be added when follicles grow less than 1 mm for more than 3 days. LH peaks are given to HCG injection for follicles larger than 14 mm, and LH peaks (early-onset LH peaks) are eliminated when the follicles are larger than 14 mm cycle. The above conditions are not included in the experimental statistics.

2.4. Statistical Analysis

SPSS13.0 software was used for statistical analysis. Count data were used for paired sample t-test; measurement data were tested with χ^2 , $P < 0.05$ was considered statistically significant.

3. Results

3.1. The Basic Situation

PCOS is characterized by hyperandrogenism, insulin resistance, and chronic anovulation and affects 5% - 10% of women in reproductive age. It is the commonest cause of anovulatory infertility accounting for >80% of all cases [2]. There was no significant difference in age, BMI, basic follicle number, and baseline LH. There was a statistically significant difference in the length of infertility and the level of basal FSH in the LE group (Table 1).

3.2. Treatment Outcomes

There were more follicles in the CC group than in the LE group. The HCG day in the LE group had lower levels of female sensation, thicker endocardium, and higher ovulation rate, the differences were statistically significant (Table 2). The clinical pregnancy rate, single pregnancy rate, and early pregnancy were all significant (Table 3).

Table 1. Basic conditions.

	BMI (kg/m ²)	Average age (years)	Infertility period (years)	Basic follicle number (one)	Basic FSH level (TU/ml)	Foundation LH level (TU/ml)
CC	24.04 ± 2.1	26.46 ± 4.6	3.7 ± 2.8	12.4 ± 3.2	6.53 ± 2.27	9.31 ± 3.76
LE	24.39 ± 2.98	27.2 ± 3.5	4.9 ± 2.6	11.9 ± 4.5	7.08 ± 1.6	8.88 ± 1.23
P value	P > 0.05	P > 0.05	P < 0.01	P > 0.05	P < 0.05	P > 0.05

Table 2. Number of ovulation monitoring.

	Cases	(Units) > 14 mm follicular	Intimal thickness	HCG daily estradiol	Ovulation rate (%)
CC	121	187	8.1 ± 1.3	326.12 ± 57.3	91 (75.2)
LH	121	161	9.5 ± 2.1	256.63 ± 62.71	107 (88.43)
P value			P < 0.01	P < 0.01	P < 0.01

Table 3. Pregnancy outcomes.

	Total clinical pregnancy rate (%)	Ovulation cycle pregnancy rate (%)	Twin pregnancy rate (%)	Number of childbirths (one)
CC	16 (13.22)	16 (17.58)	1 (6.25)	16
LH	25 (20.66)	25 (23.36)	1 (4.00)	24
P value	P < 0.05	P < 0.05		

3.3. Pregnancy

The pregnant women of the two groups had no obvious abnormalities except prenatal examinations of 3 cases of early pregnancy, 3 cases of early pregnancy, mid-late pregnancy and late pregnancy. In the CC group, there were 16 cases of pregnancy, 1 case of miscarriage in early pregnancy, 1 case of twin preterm birth, and the remaining 14 cases were single pregnancy and full-term delivery without complications. In the LE group, there were 25 cases of pregnancy, 2 cases of miscarriage in the first trimester and 1 case of twin preterm birth. One case of neonatal hypoxic-ischemic encephalopathy complicated with neonatal hypoxic-ischemic encephalopathy improved after active treatment. The remaining 22 cases were single pregnancy and full term delivery was absent (Table 3). Pregnancy and Neonatal Conditions were similar as shown in Table 4, there was no statistical difference in abortion rate between the two groups.

4. Discussion

Miwally M.F., Casper, R.F. [3] reported that 12 cases of anovulatory infertility and 10 cases of ovary infertility in PCOS patients after induction of ovulation were very thin (≤ 5 mm), given to promote ovulation after LE. The inner membrane can reach an average of 8 mm. Our study also found that the endometrial thickening in the LE group may be related to factors such as LE that do not affect the endometrial estrogen receptors, the short half-life of LE, and the increase of estrogen levels at follicular maturation. Wallace K.L., *et al.* [4] reported from the molecular biology level that compared with CC ovulation-elevating LE, it can increase the endometrium LIF, DKK1, LIFR and FGF-22 gene expression and improve endometrial receptivity. Baruah J., *et al.* [5] found that LE does not affect estrogen receptors. Binding of estrogen receptors can promote the proliferation of endometrial epithelial cells and stroma, improving the blood flow of the endometrium. Although most of the literature reported thicker endometrium in

Table 4. Pregnancy and neonatal conditions.

	Birth weight (Kg)	Score (minutes)	Complication rate (%)	Premature delivery (%)	Abortion rate (%)
CC	3.17 ± 1.54	9.57 ± 0.92	0	1 (6.67)	1 (6.25)
LH	3.14 ± 1.39	9.38 ± 0.87	1 (4.17)	1 (4.35%)	2 (8.00)
P value	P > 0.05	P > 0.05			

the LE group, the pregnancy rates reported in various literatures were not consistent. Xiao Jinsong [6] analyzed the literature on the effectiveness of letrozole in ovulation in the past decades systematically. They believe that there may be differences in the ovulation therapy of letrozole and clomiphene in many ways, as endometrium thickness, number of dominant follicles, ovulation rate, pregnancy rate, but the difference was not statistically significant. Theoretically, Letrozole can make up for the shortcomings of clomiphene ovulation therapy and provide an alternative for clinicians. However, there is still a lack of large-scale, multi-center systematic research. In 2014, Richard S., Legro, M.D. [7] found that the LE group had higher cumulative ovulation rate and birth rate than the CC group. There was no significant difference between the two groups of women in ovulation-pregnant women during pregnancy and newborns. We found that the rate of ovulation in the LE group was 88.43% higher than that in the CC group, which was 75.2%. The clinical pregnancy rate in the two groups was 20.66% compared with 13.22%, and the ovulation cycle pregnancy rate was 23.36% compared to 17.58%. There were no significant differences. The current mechanism of high LE ovulation rate is not very clear, may be related to the micro-environment of the ovary, autocrine and paracrine mechanisms, and the thickness of the endometrium is not the only factor to evaluate the endometrial receptivity, not to affect the outcome of pregnancy the only factor, therefore, the endometrial thickness is not positively correlated with the clinical pregnancy rate. In this study, multiple follicular development in LE group was less than that in CC group, and the level of estrogen in HCG day was low. Similar to the results of Polyzos *et al.* [8], it is considered that LE is beneficial to the development of single follicle in ovulation induction, reducing the multiple pregnancy rate, and reducing ovarian hypertrophy. Especially for some patients with particularly sensitive ovary, LE micro-stimulation can be used to promote ovulation, to obtain a suitable pregnancy outcome and reduce the occurrence of complications.

One possible limitation of this trial may be argued to be using pregnancy rather than live birth rate as the primary outcome. However, we believe that pregnancy rate is clinically important. A further slight concern is that more than one sonologist had done the serial ultrasonography for evaluation of endometrial thickness and follicular growth. We need to pay more attention to adverse events as well.

5. Conclusion

In summary, this study suggests that LE and CC have similar ovulation-promoting

effects, and LE may be better than CC for less multifollicular development during ovulation induction. However, whether LE can replace CC for ovulation treatment of PCOS still requires a larger sample of multicenter studies. At the same time, LE still requires a large amount of clinical data for the safety of follicles, embryos and offspring.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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