Letrozole for patients with polycystic ovary syndrome

A retrospective study

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Abstract
This retrospective study investigated the efficacy and safety of letrozole for patients with polycystic ovary syndrome (PCOS).

Totally, 136 cases of infertility women with PCOS were analyzed. Of those, 68 patients received letrozole, and were assigned to Letrozole group. The other 68 cases received clomiphene, and were assigned to clomiphene group. Patients in both groups were treated up to 5 treatment cycles. The primary endpoint included infant outcomes. The secondary endpoints consisted of the number of women in conception, pregnancy, pregnancy loss, and ovulation. In addition, any kinds of adverse events were also recorded.

Cases in the Letrozole group did not show better outcomes neither in primary endpoint (live birth, $P=.11$; birth weight, $P=.95$; infant gender, $P=.85$), nor in secondary endpoints (the number of women in conception, $P=.07$; pregnancy, $P=.12$; pregnancy loss, $P=.47$; pregnancy loss in first trimester, $P=.70$; and ovulation, $P=.09$), compared with cases in the clomiphene group. Moreover, no adverse events differ significantly between 2 groups.

This study demonstrated that the efficacy of letrozole is not superior to the clomiphene in patients with PCOS.

Abbreviation: PCOS = polycystic ovary syndrome.

Keywords: clomiphene, efficacy, letrozole, polycystic ovary syndrome

1. Introduction
Polycystic ovary syndrome (PCOS) is one of the most causes that affect the women of childbearing age,\cite{1-4} and often leads to infertility.\cite{5-7} It is diagnosed based on the hyperandrogenism, oligomenorrhea, and polycystic ovaries on ultrasonography.\cite{8-10} Its prevalence has been reported to vary from 6.8% to 18% according to the different diagnostic criteria.\cite{11,12} Its symptoms often bring psychologic disorders for patients with PCOS.\cite{13,14} These conditions often consist of depression, anxiety, irregular menstrual periods, and even the infertility.\cite{14-17}

Various management were proposed for infertile women with PCOS.\cite{18-20} However, the optimal management option has not been addressed satisfied. Although multiple treatments including weight reduction, clomiphene citrate, metformin, gonadotropins, and ovary cauterization have been reported to treat such condition, the efficacy still has insufficient evidence to support.\cite{21,22}

Letrozole is an aromatase inhibitor that was used as an ovulation inductor in anovulatory infertility women with more than 56mm endometrial thickness.\cite{23,24} It inhibits estrogen production by repressing the enzyme aromatase.\cite{25} It has been reported that letrozole can inhibit estrogen levels by at least 97% to 99%.\cite{26} The other studies also reported that letrozole is effective in clomiphene-resistant patients, and also resulted in ovulation of 62% cases, and pregnancy of 14.7%.\cite{27,28} Additionally, no adverse events have been reported on fetus.\cite{28} However, current data are still insufficient to support the idea that letrozole can be utilized effectively to treat such condition. Therefore, in this retrospective study, we investigated the efficacy and safety of letrozole for infertility women with PCOS.

2. Materials and methods

2.1. Ethics
This retrospective study was approved by the Ethical Committee of Hanzhong People’s Hospital, and The Ninth Hospital of Xi’an. It was conducted based on the Declaration of Helsinki. All patients provided the written informed consent form.

2.2. Design
A total of 136 cases of infertility women with PCOS were analyzed in this retrospective study. All cases were completed from January 2016 to December 2017 at Hanzhong People’s Hospital, and The Ninth Hospital of Xi’an. Sixty-eight cases underwent letrozole, and were assigned as a Letrozole group. The other 68 cases received clomiphene, and were assigned as a clomiphene group. No randomization and blinding were applied, except the data analyst was blinded in this study. All the cases were allocated to the different groups according to the different treatments they received. All cases in both groups received the treatment up to 5 cycles.
2.3. Patients

All cases of infertile women with PCOS from 18 to 45 years old were analyzed in this study. The PCOS was diagnosed by modified Rotterdam criteria.[25] All included cases had no major medical disorders, and their male partners were also required to participate in this study. Moreover, all subjects had ovulatory dysfunction, polycystic ovaries, or increased ovarian volume.[30,31] Furthermore, all patient cases had normal uterine cavity, and at least 1 patent fallopian tube. The sperm concentration of a male partner should have at least 14 million/mL, and both couples are committed to have regular intercourse during the study period. However, patients were excluded if they had taken confounding medications, such as primarily sex steroids, and mimic PCOS. In addition, cases were also excluded if they previously received the study medication within past 3 months.

2.4. Treatment schedule

The 68 patients in the Letrozole group received letrozole, 2.5 mg per pill daily, and the other 68 subjects in the clomiphene group taken clomiphene, 50 mg per pill daily. All patients in both groups underwent letrozole or clomiphene starting on cycle day 3 for consecutive 5 days for up to 5 menstrual cycles. If there was a nonresponse or a poor ovulatory response occurred, the dose was increased in subsequent cycles in the either group. The maximum daily dose of letrozole was 7.5 mg, and clomiphene was 150 mg.

2.5. Outcome measurements

The primary endpoint was infant outcome. The secondary endpoints comprised of the number of women in conception, pregnancy, pregnancy loss, and ovulation. Additionally, adverse events were also recorded during the treatment period.

2.6. Statistical analysis

The sample size was calculated based on the previous published study with an ovulation rate of 53.3%. Thus, the desired sample size for each group was estimated to be 68 patients with 25% difference between 2 groups, and a power of 80% in this study.

All outcome and characteristic values were analyzed by using SPSS software (SPSSV.17.0, IBM Corp, Armonk, NY). Continuous non-normally value was analyzed by Mann–Whitney U test, while normally variables were performed by t-test. Categorical value was conducted by Chi-squared test. P < .05 was defined as having a statistical significance.

3. Results

A total of 136 cases of infertile women with PCOS were analyzed in this retrospective study. All the characteristic values of included cases are showed in Table 1. No significant differences regarding all values were detected between 2 groups in this study.

The results showed that patients who received letrozole did not exert better outcomes in neither primary endpoint, including live birth (P=.11, Table 2), birth weight (P=.95, Table 2), infant gender (P=.85, Table 2); nor the secondary endpoints, comprising of the number of women in conception (P=.07, Table 3), pregnancy (P=.12, Table 3), pregnancy loss (P=.47, Table 3), pregnancy loss in first trimester (P=.70, Table 3), and ovulation (P=.09, Table 3), compared with patients who received clomiphene.

The adverse events in both groups are listed in Table 4. There were not significant differences in all adverse events between 2 groups. No treatment related death in women occurred in either group, except 1 fetal death in the clomiphene group (Table 4).

4. Discussion

Letrozole plays very important role in the treatment of infertility women with PCOS. However, its efficacy is still inconsistent, especially when compared with clomiphene.

Previous systematic review and meta-analysis reported that letrozole could significantly enhance the live birth and pregnancy rates in patients with PCOS.[34] However, the other meta-analysis did not find positive efficacy of letrozole when compared with clomiphene.[35,36] The results of the present study are consistent with the previous studies.[35,36]

The results of this retrospective study showed that no significant differences of adverse events were detected between 2 groups. In addition, patients in the Letrozole group did not exert better outcomes in primary endpoint of live birth, birth weight, and infant gender; and also in secondary endpoints of the

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**Table 1**

| Variable                          | Letrozole group (n=68) | Clomiphene group (n=68) | P    |
|----------------------------------|------------------------|-------------------------|------|
| Age, y                           | 28.3 (6.7)             | 27.5 (7.1)              | .50  |
| Race (Asian China)               | 68 (100.0)             | 68 (100.0)              | –    |
| Occupation                       |                        |                         |      |
| Employed                         | 63 (92.6)              | 60 (88.2)               | .39  |
| Unemployed                       | 5 (7.4)                | 8 (11.8)                | –    |
| Body mass index                  | 28.4 (3.3)             | 27.8 (3.7)              | .32  |
| Duration of infertility, y       | 4.3 (3.2)              | 4.6 (3.4)               | .60  |
| Oligomenorrhea                   | 51 (75.0)              | 55 (80.9)               | .41  |
| Menometrorrhagia                 | 2 (2.9)                | 3 (4.4)                 | .65  |
| Regular menstruation             | 15 (22.1)              | 10 (14.7)               | .27  |
| Hirsutism                        | 20 (29.4)              | 18 (26.5)               | .70  |
| History of previous miscarriage  | 16 (23.5)              | 15 (21.1)               | .84  |
| Mean luteinizing hormone on day 3 of menstruation, mlU/mL | 10.1 (4.0) | 10.0 (4.2) | .89  |
| Mean follicle-stimulating hormone on day 3 of menstruation, mlU/mL | 5.3 (1.9) | 5.2 (2.1) | .77  |
| Mean thyroid-stimulating hormone, mlU/mL | 1.8 (0.8) | 1.9 (0.7) | .44  |
| Mean estradiol on day 3 of menstruation, pg/mL | 91.1 (22.4) | 90.7 (21.8) | .92  |

Data are present as mean ± standard deviation or number.

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**Table 2**

| Primary endpoints | Letrozole group (n=68) | Clomiphene group (n=68) | P    |
|-------------------|------------------------|-------------------------|------|
| Live birth        | 20 (29.4)              | 12 (17.6)               | .11  |
| Singleton         | 18/20 (90.0)           | 12/12 (100.0)           | .44  |
| Twin              | 22/20 (10.0)           | 0/12 (0)                | –    |
| Birth weight, g   | 3261.7 (533.6)         | 3246.0 (801.4)          | .95  |
| Infant gender     |                        |                         |      |
| Male              | 11/20 (55.0)           | 7/12 (58.3)             | .85  |
| Female            | 9/20 (45.0)            | 5/12 (41.7)             | –    |

Data are present as mean ± standard deviation or number (%).
Comparison of adverse events between 2 groups.

| Adverse events          | Letrozole group (n=68) | Clomiphene group (n=68) | P    |
|-------------------------|-----------------------|-------------------------|------|
| Hot flushes             | 15 (22.1)             | 23 (33.8)               | .13  |
| Fatigue                 | 15 (22.1)             | 9 (13.2)                | .18  |
| Dizziness               | 8 (11.8)              | 5 (7.4)                 | .39  |
| Ectopic pregnancy       | 1 (1.5)               | 0 (0)                   | .50  |
| Heterotrophic pregnancy | 0 (0)                 | 1 (1.5)                 | .50  |
| Hospitalization         | 1 (1.5)               | 2 (2.9)                 | .57  |
| Congenital anomaly      | 1 (1.5)               | 0 (0)                   | .50  |
| Fetal death             | 0 (0)                 | 1 (1.5)                 | .50  |

Data are present as mean (range).

Comparison of secondary endpoints between 2 groups.

| Secondary endpoints                     | Letrozole group (n=68) | Clomiphene group (n=68) | P    |
|-----------------------------------------|-----------------------|-------------------------|------|
| No. of women with conception            | 27 (39.7)             | 17 (25.9)               | .07  |
| No. of women with pregnancy             | 22 (32.4)             | 14 (20.6)               | .12  |
| No. of women with pregnancy loss in first trimester | 5 (7.4)             | 3 (4.4)                 | .47  |
| No. of women with ovulation             | 4 (5.9)               | 3 (4.4)                 | .70  |
| No. of women with ovulation             | 59 (86.8)             | 51 (75.0)               | .09  |

Data are present as number (%).

number of women with conception, pregnancy, pregnancy loss, pregnancy loss in first trimester, and ovulation, compared with subjects in the clomiphene group. Additionally, no significant differences in adverse events were found between 2 groups. It indicated that letrozole and clomiphene have similar efficacy and safety in treating infertility women with PCOS.

This retrospective study had several following limitations. First of all, the sample size was still relative small, which may affect the results of this study. Then, this retrospective study had its own intrinsic limitation, which may impact its results. Thirdly, this study did not include comprehensive endpoints, such as quality of life in infertility women with PCOS, because it just analyzed the outcomes data based on the completed cases only. Fourth, this study did not utilize randomization and blinding, which may increase the risk of case selection. Therefore, the future studies should avoid all these limitations.

5. Conclusion

The results of this retrospective study did not find that the efficacy of letrozole is superior to clomiphene for the treatment of infertility women with PCOS.

Author contributions

Conceptualization: Jun Shi, Hui-juan Guang, Feng Li.
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