ORIGINAL REPORT

Comparison of Treatment Outcomes of Infertile Women by Clomiphene Citrate and Letrozole with Gonadotropins Underwent Intrauterine Insemination

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Received: 21 Aug. 2010; Received in revised form: 1 Sep. 2010; Accepted: 14 Sep. 2010

Abstract- This study was designed to compare the effect of clomiphene and letrozole in ovulatory stimulation in infertile women under intrauterine insemination who referred to Mahdiyeh infertility clinic during 2008-2009. 106 infertile women were randomly divided into two equal groups. Patients were treated with 5 mg of letrozole daily (in letrozole group) or 100 mg of clomiphene citrate daily (in clomiphene group) for five days starting on day 3 of their menses. Dose and time of FSH was similar in the two groups. Number of follicles, endometrial thickness, Pregnancy rate and prevalence of complications were compared in the two groups. Mean (±SD) of age in letrozole and clomiphene groups was 26.3±3.9 and 25.2±4.9 respectively (*P*=0.186). Average number of follicles was 2.5±1.65 in letrozole group and 2.36 ± 1.4 in clomiphene group (*P*=0.764). β-hCG was positive in 11 (20.8%) in letrozole and 12 (22.6%) in clomiphene groups (*P*=0.814). Pregnancy rate was 20.8% and 22.6% in letrozole and clomiphene group respectively (*P*=0.814). There was no difference in rate of abortion between groups. Endometrial thickness (ET) at the time of hCG administration in the letrozole (6.8±1.5 mm) and in clomiphene (6.6±1.2 mm) (*P*=0.615). But ET>7.4 mm was found in 2 cased (3.8%) in clomiphene group and 12 cases (%22.8) in letrozole groups (*P*=0.01). It appears that letrozole and clomiphene have similar outcome infertile women under intrauterine insemination and these drugs are good alternative for each others.

Acta Medica Iranica, 2012; 50(1): 18-20.

Keywords : Letrozole; Clomiphene citrate; Infertility; Gonadotropin

Introduction

Ovulatory dysfunction consists of 15% of infertility causes (1). Clomiphene citrate is the most commonly prescribed agent for induction of ovulation for the treatment of subfertility associated with oligo-ovulation (2) and could be used as a super ovulation regiment for intrauterine insemination (IUI) cycle, when favorably combined with exogenous gonadotropins. Otherwise patients with unexplained infertility with a frequency rate of 10-15% are offered controlled ovarian hyper stimulation combined with IUI as the first line therapy (3).

It has recently been suggested that a group of highly selective aromatase inhibitors, including letrozole, that suppress estrogen biosynthesis may successfully substitute for clomiphene citrate in controlled ovarian hyperstimulation regiment in this group of infertile women (4-6). Letrozole may have advantages over clomiphene citrate. The main advantage is not having anti-estrogenic effect that can be seen in use of clomiphene citrate. Letrozole has a shorter half-life, no adverse effects on endometrium and no effect on cervical mucosa (7).

Reduced risk of multiple pregnancies is also added to these advantages. In some studies carried out to compare the hormonal and therapeutic outcomes of these drugs showed no difference in pregnancy outcome (8,9) while some other investigators reported better effect for letrozole (10).

In other hand some studies introduced letrozole as the first drug of choice due to its advantages on reduced risk of multiple pregnancies (11,12). This study was aimed to compare the effect of clomiphene and letrozole in ovulatory stimulation in infertile women.

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Table 1. Demographic characteristics of patients treated with Clomiphen citrate and Letrozole.

Variable	Clomiphene citrate + FSH (n=53)	Letrozole + FSH (n=53)	Significance
Age	25.7±4.6	26.7±3.4	N.S.
BMI (Kg/m^2)	25.2±4.9	26.3±3.9	N.S.
Duration of infertility	4.6±2.5	5.3 ±2	N.S.
Day 3 FSH (mIU/ml)	6.4±2.2	5.5 ±2.1	N.S.
Day 3 LH (mIU/ml)	8.8±9.7	7.4±7.1	N.S.
Day 3 E_2 (pg/ml)	86.4±29.5	85.9±27.9	N.S.

Materials and Methods

In this randomized clinical trial, one hundred six infertile couples eligible for super ovulation and intrauterine insemination (IUI) for first time were recruited. All couples underwent a routine workup in Mahdieh Infertility Clinic. The inclusion criteria were female age<36 years old, tubal patency confirmed by hysterosalpingography, mild oligoasthenospermia and the group of patients with unexplained infertility, and those with severe male factor infertility, endometriosis, tubal factor were not included.

The patients were randomized in two groups. The patients in letrozole group received 5 mg letrozole for 5 days (from day 3 to 7 of menstrual cycle). In the clomiphene group clomiphene citrate 100 mg was given for 5 days from day 3 of menstrual cycle. In addition, recombinant FSH (Fostimon) 75 IU was administrated the following two days. Before starting the stimulation course a transvaginal sonograhpy on day 2 or 3 of menstrual cycle was done to monitor ovaries and endometrial thickness by the same radiologist, and repeated 2-3 times during the treatment course to monitor the ovarian response and endometrial thickness. When 2-3 mature follicles reached >=16-18 mm in diameter hCG was given in a dose of 10000 IU and IUI was performed 36-40 hours later. Progesterone (suppository or injection) was administrated in both groups for the luteal phase support.

The clinical pregnancy was defined when there was a positive titer of β-hCG and an intrauterine gestational sac(s) was visible on ultrasonography. SPSS 16 software was used for statistical analysis. *P* value less than 0.05 was considered statistically significant.

Results

A total of 106 patients: 53 patients in letrozole and 53 patients in clomiphene citrate group meeting inclusion criteria in this study. Demographic characteristics showed no significant differences (Table 1). Patients receiving letrozole showed no significant difference in endometrial thickness on the day of hCG administration with patients receiving clomiphene citrate (6.8 ± 1.5 mm in contrast with 6.6 ± 1.2 mm, *P*=0.615).

The number of mature follicles at the time of hCG were not different between two groups (2.51±1.65 in letrozole and 2.36±1.4 in clomiphene citrate group, *P*=0.764).

There was no difference between groups in pregnancy outcome (20.8% and 22.6% in letrozole and clomiphene citrate respectively, *P*=0.501).

Twin pregnancy was occurred in one pregnant woman in clomiphene citrate group and a triple pregnancy was occurred in letrozole group. Four out of 12 pregnant women in the clomiphene citrate group (33.3%) and 2 out of 11 pregnant cases in the letrozole group (18.2%) experienced abortion. There was no occurrence of ectopic pregnancy. Ovarian hyper stimulation syndrome was occurred in one patient of each group.

Discussion

In our study letrozole group showed no difference in pregnancy rate comparing with clomiphene group, although there was higher rate of abortion. Some studies also reported no significant difference in pregnancy rate between two groups (8,9,12-14). The higher rate of abortion in clomiphene citrate group was reported in some of these studies (8,12). Fewer studies have addressed the potential impact of aromatase inhibitors on implantation and pregnancy outcome (10).

This study showed no significant difference in endometrial thickness between letrozole and clomiphene citrate, it is similar to the studies carried out by Jee *et al*. (9), Al-Fazan *et al*. (8) and Ghazizadeh *et al*. (12). But contrary to these studies and our study suggesting no

higher effect of letrozole on endometrium, there are also some reports in the literature showing a beneficial effect of letrozole in this regard (10,15). Another study also showed that clomiphene citrate causes inadequate endometrial thickness in 15-50% of patients and have negative effect on the quality of the cervical and endometrial mucosa (16) and attributed these complications to the anti-estrogenic effect and the relatively longer half-life of clomiphene citrate (17).

According to the results of the present study the numbers of mature follicles were not different between two groups of study. Some studies reported similar results (6,8,15) while some have reported higher number of mature follicles in clomiphene citrate group (9,12,14).

In our study multiple pregnancy was comparable in both groups in contrast some researches showed higher risk of multiple pregnancy induced by clomiphene citrate (13). In conclusion, this study found no beneficial effect for an aromatase inhibitor to clomiphene citrate and suggests selecting these drugs according to the cost effectiveness, duration of therapy, characteristics and compliance of patients although this issue can be examined in further prospective and randomized studies.

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