

# The Impact of Letrozole Versus Clomiphene Citrate on Uterine Blood Flow in Patients with Unexplained Infertility

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## Abstract

**Objective:** To compare the effectiveness of letrozole and clomiphene citrate (CC) on uterine blood flow rate in patients with unexplained infertility.

**Materials and methods:** In this randomized clinical trial 90 women with unexplained infertility referred to a university clinic from January 2011- December 2013 were enrolled. Thirty patients were randomized for letrozole, 30 patients for CC and 30 patients for control group. On the day 3 of cycle the patients were given letrozole 2.5mg/day or CC 100 mg /day orally or did not receive any treatment. Resistance index (RI) and pulsatility index (PI) of uterine artery were calculated and chemical pregnancy rate was evaluated.

**Results:** Mean age was  $26.4 \pm 3.2$  (20-33) and mean BMI was  $26.3 \pm 3.2$ . After treatment using ultrasonography the Resistance index (RI) and Pulsatility index (PI) showed no significant difference among three groups ( $P > 0.05$ ). Pregnancy rate in letrozole group (58%) was more in comparison to CC (53.6%) and control groups (46%) but the difference was not significant ( $P > 0.05$ ).

**Conclusion:** Our study showed that letrozole and clomiphene citrate have comparable impact on uterine blood flow and pregnancy rate in women with unexplained infertility.

**Keywords:** Uterine Blood Flow, Letrozole, Clomiphene Citrate, Ovulation Induction, Unexplained Infertility

## Introduction

Unexplained infertility (UI) is the frequent infertility diagnosis given to women and encompassing up to approximately 15- 30% of all cases (1). Unexplained infertility diagnosis is made after testing fails to detect any abnormality. Therefore, the treatment for unexplained infertility is empiric because it does not address a precise impairment or functional defect (1). Clomiphene citrate and intrauterine insemination (IUI), controlled ovarian hyperstimulation (COH)

with IUI, IVF expectant observation with timed intercourse and lifestyle changes are the most frequent treatments for unexplained infertility (2, 3). It has been proposed that the uterine blood flow affects the uterine receptivity (4) and it has been believed that the pulsatility index (blood flow impedance in the uterine arteries) is valuable in measuring endometrial receptivity (5, 6).

Clomiphene citrate (CC) has been presented in 1960 and widely used in infertility treatment (7). Now it is used in the anovulatory treatment and unexplained infertility either alone or in combination with HMG or recombinant FSH (8).

The rate of ovulation in previous experiences using clomiphene has been about 60%–85% and

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10%–20% pregnancy rate per cycle (9, 10). However resistance to CC occurs on 15-20%, moreover it may negatively affect cervical mucus and endometrium and it is related with difference between ovulation and conception rates (11, 12).

Letrozole is an alternative treatment for unexplained infertility and it is an aromatase inhibitor that suppresses intratumoral systemic production of estrone from androstenedione (13, 14). An experience with letrozole on rats divulged more than 80% ovarian E2 levels suppression and remarkable increasing in LH and FSH, furthermore it increased ovarian weights about 35% within 1 week of treatment (15). Although the effect of letrozole and CC in patients with infertility are studied in many different ways the impact of these agents on endometrial blood flow on Iranian women with unexplained infertility are not evaluate. This controlled clinical trial was steered to compare the effectiveness of letrozole and CC on blood flow in patients with unexplained infertility.

## Materials and methods

In this randomized clinical trial 90 women with unexplained fertility referred to Ali -ibn-e- Abitaleb clinic affiliated to Zahedan University of medical sciences in from January to December 2011 were enrolled. Including criteria were: women with unexplained infertility lasting more than 1 year, age more than 25 and less than 35 years, BMI >19 kg/m<sup>2</sup> and <30 kg/m<sup>2</sup>, normal cycles, at least one open tube in hysterosalpingography (HSG), normal male factor, documentation of ovulation with midluteal serum progesterone levels exceeding 5 ng/mL, normal hormonal profile (TSH, PRL, T, and DHEAS), and day 3 FSH ≤12 IU/L. Unexplained infertility was diagnosed based on a normal semen analysis according to World Health Organization criteria (16). On the other hand the patients were excluded if they have experienced ART (assistant reproductive technology), cervicitis, age more than 35 and BMI

>30. There was no history of underlying disease and surgery, moreover hysterosalpingography (HSG) did not detect any abnormality. Additionally to rule out the male factor the semen of husband of all patients were analyzed and did not show any abnormality.

The study procedure was explained for all women and informed written consents were given. The study protocol was approved by ethical committee of Zahedan University of medical sciences.

To randomization, the blocks of six were used and two patients of each block were selected for each group. In this regard 30 patients were selected for letrozole, 30 patients CC and 30 patients were selected as a control group.

Initially the demographic and clinical data of patients were record and patients were visited by obstetrics and gynecologist specialist. Then on the day 3 of cycle the patients were given letrozole 2.5mg/day and CC 100 mg /day orally in letrozole and CC groups respectively, but patients in control group did not receive any treatment to ovulation induction.

To measurement of uterine blood flow, resistance index (RI) and pulsatility index (PI) of uterine were calculated moreover to evaluate the pregnancy rate βHCG was measured.

Data were analyzed using SPSS version 20. Categorical data are presented as numbers (%), and continuous data as mean ± SD. We used the Chi<sub>2</sub> or Fisher's exact test to compare categorical variables and the Student's *t* test to compare continuous variables.

## Results

Totally we evaluated 90 patients in three groups with Mean age 26.4±3.2 (20-33) and mean BMI 26.3± 3.2. The demographic and clinical data in three groups are detailed in table 1.

After treatment the Resistance index (RI) and Pulsatility index (PI) uterine artery were measured using ultrasonography. The difference between three groups was not significant (P>0.05) (table 2).

**Table 1:** The demographic and clinical data in three groups

| Groups                   | Letrozole  | CC          | Control    | P value |
|--------------------------|------------|-------------|------------|---------|
| Age                      | 23.1 ± 2.3 | 23.07 ± 1.5 | 22.9 ± 1.3 | NS      |
| BMI                      | 26.8 ± 3.6 | 26.6 ± 3.51 | 25.8 ± 2.7 | NS      |
| Cycle days               | 5.3 ± 1    | 5.2 ± 0.7   | 4.9 ± 0.5  | 0.006   |
| Interval between cycles  | 29.4 ± 3.5 | 31.4 ± 2.9  | 30 ± 3.3   | NS      |
| Infertility time (years) | 4.2 ± 1.8  | 3.4 ± 3     | 3 ± 0.8    | 0.07    |
| Nulipar                  | 86.6 %     | 80%         | 73.3 %     | NS      |
| Multipar                 | 13.4 %     | 20%         | 26.7 %     | NS      |

**Table 2:** Resistance index (RI) Pulsatility index (PI)

| Groups                 | letrozole  | CC          | Control     | p value |
|------------------------|------------|-------------|-------------|---------|
| Resistance index (RI)  | 0.85 ± 0.2 | 0.85 ± 0.03 | 1.01 ± 0.02 | NS      |
| Pulsatility index (PI) | 2.8 ± 0.04 | 2.4 ± 0.04  | 2.6 ± 0.02  | NS      |

The pregnancy rate in letrozole group (58%) was more than CC (53.6%) and control groups (46%) but the difference was not significant ( $P>0.05$ ) (table 3).

**Table 3:** The pregnancy rate on three groups

| Groups             | letrozole | CC    | Control | p value |
|--------------------|-----------|-------|---------|---------|
| β-HCG positive     | 58%       | 53.6% | 46%     | NS      |
| β-HCG negative     | 39%       | 46.7% | 53.3%   | NS      |
| β-HCG intermediate | 3%        | -     | -       | -       |

## Discussion

Previous studies have been examined some ultrasonographic indicators as endometrium blood flow, uterine artery, endometrial thickness and endometrial pattern for evaluation of receptivity of endometrium. The most of these surveys have reported that sufficient uterine perfusion increased the endometrial receptivity and pregnancy rate (16-18). Another study by Kupesic et al specified that endometrial perfusion performs the implantation success rate and exposes the problem of unexplained infertility (17). Additionally another study by Chien et al. signified mean PI and RI value in pregnant women was lower than nonpregnant (18).

Clomiphene is a non-steroidal agent and blocks estrogenic hypothalamic receptors, moreover it has peripheral anti estrogenic activity on endometrium and cervical mucus (19). Letrozole, is a selective aromatase inhibitor and increases FSH secretion from the anterior pituitary (20). However letrozole has not anti-estrogenic peripheral activity, furthermore it is cleared from the circulation more rapidly than clomiphene citrate (half-life 48 hours for letrozole vs. 2 weeks for CC) (21). Based on our knowledge the impact of CC and letrozole on endometrium blood flow in Iranian women with unexplained infertility did not study before. So in this controlled clinical trial we evaluated the effect of letrozole and clomiphene citrate on endometrium blood flow. We measured the pulsatility index, resistance index and pregnancy rate in 90 women. The results did not indicate significant difference between three groups regarding pulsatility index, resistance index and pregnancy rate. In line with our study Bayar et al in a randomized controlled trial (RCT) compared

letrozole with clomiphene citrate and indicated no significant difference in either the ovulation rate or the clinical pregnancy rate between the two groups (22). Furthermore another largest RCT by Badawy et al compared letrozole versus clomiphene on women with PCOS (poly cystic ovary syndrome) and specified that the ovulation and pregnancy rates between the two groups was comparable, however the endometrial thickness in clomiphene group was meaningfully higher than letrozole group (23). Additionally, in agreement to our results Jee et al compared the clinical outcomes between letrozole and clomiphene citrate (CC) in gonadotropin combined intrauterine insemination (IUI) cycles in 93 infertile women and implied that letrozole produce a comparable pregnancy rate vs. CC in gonadotropin combined IUI cycles (24).

In contrast to our findings Atay et al compared letrozole (2.5 mgs) with clomiphene citrate (100 mgs/day) in 106 women with PCOS and designated that the ovulation rate and the clinical pregnancy rate were significantly higher in the letrozole than clomiphene group. Moreover the authors advised letrozole as a better first line treatment in these patients (25). Consistently another study by Jirge et al compared endocrine and follicular dynamics in 30 ovulatory volunteer women in natural cycles and cycles stimulated with clomiphene or letrozole and pointed out that the shorter follicular phase and less multiple follicular development in letrozole than CC group, however the ovulation profiles were similar in all cycles (26).

The most of studies that we reviewed in this article were consistent with our experience and emphasized that two agents have relatively equal effect on ovulation and pregnancy rate in unexplained infertile women. However mono follicular cycles in letrozole group was more than CC in some studies (27). Moreover some of these studies indicated that endometrial thickening in letrozole group was higher than CC (28). Additionally another study showed letrozole increase the endometrial thickening more than CC without any adverse effect (29). These findings confirm the hypotheses that declare lack of peripheral anti estrogenic effect of letrozole.

The main limitation of our study is the relatively small sample size so further investigations are recommended with larger series to validate the findings reported here.

In conclusion our study confirmed the previous reports and showed that letrozole and clomiphene citrate have comparable impact on uterine blood flow and pregnancy rate in women with unexplained infertility.

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