Comparison of The Efficacy of Letrozole and Gonadotropin Combination Versus Gonadotropin Alone In Intrauterine Insemination Cycles In Patients With Unexplained Infertility

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ABSTRACT

This study aimed to determine the outcomes of combined treatment of letrozole (LTZ) with recombinant follicle-stimulating hormone (rFSH) in comparison with rFSH alone in intrauterine insemination (IUI) cycles.
This study consisted of 86 patients who experienced 106 IUI cycles. Patients were classified into two treatment groups: group I underwent a combination of LTZ plus rFSH, and group II received rFSH alone. Ovulation was triggered with human chorionic gonadotropin (hCG), and IUI performed 36 hours later. The number of follicles ≥18 mm, endometrial thickness, required dose of FSH, duration of ovulation induction (OI), clinical pregnancy rates, multiple pregnancy rates, spontaneous abortion rates, and live birth rates were evaluated.
The total required rFSH dose during the OI was significantly lower in the LTZ-rFSH combination group than the rFSH alone group (401.2±177.1 IU and 770.1±345.8 IU, respectively, p<0.001). The days of stimulation with rFSH were also lower in the LTZ co-treatment group than the rFSH-alone group (5.2±1.3 days and 10.1±3.0 days, respectively, p<0.001). Clinical pregnancy rate was 17.0% in LTZ-rFSH group, and 15.2% in rFSH group (p>0.05).
The combined use of LTZ with rFSH resulted in a lower required dose of rFSH, a similar and acceptable endometrial thickness at the day of hCG administration, and comparable pregnancy rate compared with rFSH alone.

Key Words: Letrozole, gonadotropin, ovulation induction, intrauterine insemination

Introduction

Intrauterine insemination (IUI) is frequently practiced as first-line treatment for couples with unexplained or mild male-factor infertility worldwide because it is considered to increase the pregnancy rates while simple to perform and to be comparatively low-cost (1). It is possible to perform the IUI procedure in patients' natural cycles (2). But, it was found that pregnancy and live birth rates in IUI cycles were significantly higher with ovulation induction (OI) cycles using medications compared with no stimulation for couples with infertility (1,3). Also, there are conflicts among clinicians on the appropriate ovarian stimulation protocol in an IUI cycle.

Clomiphene citrate (CC) has been accepted as a standard treatment for ovarian hyperstimulation in unexplained infertility for many years (4,5). Clomiphene citrate increases the release of FSH from the pituitary by blocking estrogen negative feedback effect, and thus increases the follicle development (6). However, CC has disadvantages in treatment, and the prevalence of CC resistance is 15-40% (7). Clomiphene citrate depletes estrogen receptors and has a long half-life (2

weeks), inducing unfavorable effects on endometrial thickness and cervical mucus (8,9). This effect leads to a pregnancy rate of 8.5-10% per cycle with the combination of CC and IUI, despite the high ovulation rate with CC (10).

In gonadotropin-stimulated IUI cycles, the pregnancy rates were in the range of 15-17% per cycle (11,12). Nevertheless, the use of gonadotropin significantly boosts the cost of treatment and increases the risk of ovarian hyperstimulation syndrome and multiple pregnancies (13). With the combination of gonadotropin and CC in IUI cycles, the required gonadotropin dose and treatment cost decrease compared to gonadotropin use alone, but the pregnancy rates are low with this combination due to the anti-estrogenic effects of CC (14).

Letrozole (LTZ), an aromatase inhibitor, inhibits the conversion of androgens to estrogens in ovarian follicles, resulting in a decrease in circulating and local estrogens and an increase in intraovarian androgens (9). The reduction in estrogen levels causes the discharge of the hypothalamic-pituitary axis from the negative feedback of estrogen. This effect leads to an increase in FSH release, which results in follicular growth (9). Unlike CC, LTZ has no anti-estrogenic impact and has a short (45 hour) half-life (15). Due to these effects, LTZ does not cause an unfavorable effect on cervical mucus and endometrial thickness, and therefore, LTZ correlated with higher pregnancy rates (9). letrozole and gonadotropin combination can diminish the required dose of FSH for ovarian stimulation without jeopardizing the pregnancy rate compared with FSH alone and result in a low occurrence of multiple gestations and ovarian hyperstimulation syndrome (OHSS) (16).

This study aimed to examine the effectiveness of LTZ-gonadotropin combination to gonadotropins as an ovulation induction therapy for unexplained infertility couples in IUI cycles.

Material and Methods

Patients: This retrospective study included 86 women with unexplained infertility ranging in age from 20 to 40 years who admitted to Gazi Yaşargil Training and Research Hospital Infertility policlinic between February 2017 and March 2018. The clinical data were recorded from our clinical database. All the patients had unexplained infertility and experienced ovarian hyperstimulation with recombinant FSH (rFSH) alone or combined with LTZ (5.0 mg/day) for

IUI. The Ethics Committee of Gazi Yaşargil Training and Research Hospital approved the study.

Before the treatment, all couples received a regular infertility assessment that involved transvaginal ultrasonography (US), a baseline hormone levels that included FSH, LH, estradiol, PRL, and TSH in the early follicular stage, a semen analysis, and assessment of tubal patency by hysterosalpingogram or laparoscopy. Ovulation documented by serum progesterone on day 21. The determination of unexplained infertility was based on eliminating female and male factor infertility. The inclusion criteria were as follows: aged <40 years, infertility of at least one-year continuance, at least one patent fallopian tube, a healthy uterine cavity, and at least 15 million of motile sperm/mL with ≥32% of progressive motility and ≥4% of normal morphology in the spouses' semen analysis. The exclusion criteria were as follows: oligo/anovulation, bilateral tubal pathology, other endocrine disorders, and male factor infertility. Canceled cycles were also excluded.

Study Groups: This study consisted of 86 women who underwent 106 IUI cycles. None of the women had treated with LTZ before. Patients were informed entirely about the mechanism of effect and the experiential essence of LTZ. The off-label indication of LTZ was wholly explained. The use of LTZ was based on the couple's choice. Participants were classified into two treatment groups: group I received a combination of LTZ (Femara; Novartis, Basel, Switzerland) plus rFSH (Gonal-F; Merck, Aubonne, Switzerland), and group II received rFSH (Gonal-F; Merck, Aubonne, Switzerland) alone. Group I included 34 patients who had 47 OI cycles. Group II included 52 patients who had 59 OI cycles. All women experienced a maximum of two cycles of IUI. The initial dose of gonadotropins was determined on the clinical characteristics of women, including age, BMI, duration of infertility, and prior treatment cycles. In group I, LTZ was given 5.0 mg/day from day 3 to 7 of the menstrual cycle, followed by the rFSH dose beginning at 50-150 IU/day starting on day seven until the day of the hCG administration. In group II, rFSH treatment was begun on day 3 of the menstrual period with an initial dose of 50-150 IU/day until the day of the hCG treatment. Both of the groups, the dose of rFSH was adjusted depending on the ovarian response to achieve mature follicle (≥18 mm). Follicle growth (the number and the diameter of follicles) was monitored with transvaginal

ultrasound by gynecologists from day 7 to day 10 of the cycle, and then performed every two days based on the follicle growth. When the diameter of at least one follicle had reached 18mm, a subcutaneous injection of 6500 IU of hCG (Ovitrelle; Merck, Modugno, Italy) was used to trigger ovulation. The endometrial thickness was evaluated at the same time as in the plane through the longitudinal axis of the uterus. A single IUI was conducted 36 hours after hCG administration. Cycles were offered to cancel when more than four ≥18 mm follicles were seen.

Intrauterine Insemination: On IUI day, semen was obtained at the laboratory after the 3-6 days of sexual abstinence period, prepared with density-gradient centrifugation after liquefaction. 0.5 mL of washed semen sample was filled into a flexible catheter. After the evaluation of sperm count and motility, the IUI was conducted by a gynecologist. Patients were offered to rest for 30 minutes after IUI. All patients received 200 mg progesterone (Progestan; Koçak, Istanbul, Turkey) twice a day for luteal phase support after IUI until the day of hCG testing.

The serum β-hCG was measured two weeks after the IUI procedure for the diagnosis of pregnancy if the menstrual bleeding was delayed. Clinical pregnancy was confirmed by the definition of intrauterine fetal heartbeat in the US examination two weeks after a positive pregnancy test. Multiple pregnancies were defined as more than one intrauterine fetal heartbeat observed. Spontaneous abortion was defined as the loss of the pregnancy before the 12 6/7 weeks of gestation. Live birth was defined as the birth of an infant after 24 weeks of gestation who breathes with a heartbeat.

The primary outcomes of the study were the number of follicles ≥18 mm, endometrial thickness, required dose of FSH, duration of OI, clinical pregnancy rates, and multiple pregnancy rates. Spontaneous abortion rates and live birth rates were also evaluated.

Statistics: IBM SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) statistical package program was used for statistical evaluation of our research data. Measured variables were presented as mean±standard deviation (std), and categorical variables were presented as numbers and percentages (%). Kolmogorov-Smirnov test was used to determine whether the numerical data matched the normality distribution. Mann-Whitney U test was used to compare the non-normally distributed data. A Chi-square test was used to compare qualitative variables. P-value <0.05 was considered statistically significant.

Results

A total of 86 patients experienced 106 IUI cycles. All participants diagnosed with unexplained infertility. There were no statistically significant differences between the two groups in terms of demographic characteristics included age, BMI, and duration of infertility (Table 1). Antral follicle count and baseline laboratory values included FSH, LH, estradiol, prolactin, and TSH were statistically similar in both groups. These results confirm the homogeneousness of the therapy groups.

The clinical outcomes of the patients are summarized in Table 2. The total required rFSH dose during the OI was significantly lower in the LTZ-rFSH combination group than the rFSH alone group (p<0.001). The days of stimulation with rFSH were also lower in the LTZ co-treatment group than the rFSH-alone group (p<0.001).

When the groups were compared in terms of the number of follicles with diameter ≥18 mm and endometrial thickness by the day of the hCG administration, there was no statistically significant difference between them (p>0.05 and p>0.05, respectively). OHSS was not observed in patients in both groups.

Clinical pregnancy rate was 17.0% in LTZ-rFSH group, and 15.2% in rFSH group. The clinical pregnancy rate was slightly higher in the LTZ co-treatment group, but this was not statistically significant (p>0.05).

While multiple gestations were not seen in the LTZ-rFSH group, three multiple gestations (twin) occurred in the rFSH alone group (p>0.05). When the outcomes of multiple pregnancies were examined, one of them ended in abortion, while one was delivered at 34th weeks, and the other was delivered at term. No ectopic pregnancy occurred in either group. There were two miscarriages in the LTZ co-treatment group, four miscarriages in the rFSH alone group. There was one preterm delivery in the LTZ-rFSH group, which was at the 33rd week of pregnancy. There was one preterm delivery in the rFSH alone group, which was the twin pregnancy that was delivered at the 34th week of pregnancy. No fetal anomaly, stillbirth, or neonatal death occurred in any group. There were no significant differences between the two groups in terms of the gestational week at delivery, birth weight, and the newborn's first and fifth minute Apgar score values (Table 3).

Table 1. Baseline characteristics and laboratory values of the patients

	Group I LTZ+rFSH (No. of patients= 34)	Group II rFSH (No. of patients= 52)	P value
Age (years)	31.5±5.9	30.8±4.4	0.898
BMI (kg/m2)	25.5±2.5	24.8±2.8	0.116
Primary infertility, n (%)	23 (63.8%)	34 (65.3%)	0.236
Duration of infertility (years)	4.8±3.8	3.7±2.8	0.254
	3 (1-16)	2.5 (1-16)	
Antral follicle count	15.7±8.1	16.7±7.7	0.410
	14 (6-29)	17 (7-30)	
FSH (mIU/mL)	6.3±1.8	6.1±1.7	0.620
LH (mIU/mL)	4.9±2.3	5.1±1.6	0.840
Estradiol (pg/mL)	36.4±13.5	36.2±11.2	0.958
Prolactine (ng/mL)	10.9±5.0	13.5±6.7	0.164
TSH (mU/L)	1.9±0.8	2.1±1.0	0.138

Measured variables were presented as mean±standard deviation and categorical variables were presented as numbers and percentages (%). For statistical analysis, Kolmogorov-Smirnov and Mann-Whitney U tests were used.

Table 2. Clinical outcomes of the patients

	Group I LTZ+rFSH (No.of cycles=47)	Group II rFSH (No. of cycles=59)	P value
Days of stimulation with rFSH	5.2±1.3	10.1±3.0	**<0.001***
Dose of rFSH, IU	401.2±177.1	770.1±345.8	**<0.001***
Number of follicles ≥18 mm	1.6±0.7	1.6±0.8	0.853
	1 (1-3)	1 (1-3)	
Endometrial thickness, mm	8.7±1.9	9.2±2.2	0.290
Clinical pregnancy, n (%)	8 (17.0%)	9 (15.2)	0.330
Spontaneous abortion, n (%)	2 (4.2%)	4 (6.7%)	0.373
Live birth, n (%)	6 (12.8%)	5 (8.5%)	0.222
Multiple pregnancies, n (%)	0	3 (5.1%)	0.061

Measured variables were presented as mean±standard deviation, and categorical variables were presented as numbers and percentages (%). For statistical analysis, Kolmogorov-Smirnov, Chi-square, and Mann-Whitney U tests were used. ***: p<0.001

Table 3. Neonatal outcomes of the groups

	Group I LTZ+rFSH (No.of cycles=47)	Group II rFSH (No. of cycles=59)	P value
Gestational week at delivery	38.1±2.8	37.2±2.6	0.476
Birthweight (g)	3028.0±352.2	2956±374.6	0.358
1st minute Apgar score	8.6±1.2	8.5±1.2	0.626
5th minute Apgar score	9.2±0.6	9.2±0.4	0.830

Measured variables were presented as mean±standard deviation. For statistical analysis, Kolmogorov-Smirnov and Mann-Whitney U tests were used.

Discussion

In our study, we present our findings with the combined use of LTZ and rFSH in unexplained infertility couples in IUI cycles.

Gonadotropins are widely used in OI during IUI cycles. A meta-analysis reported that exogenous gonadotropins increase pregnancy rates and live birth rates compared to the natural cycle or other OI drugs (17). However, the use of gonadotropins can cause adverse effects such as multiple pregnancies or OHSS and raised the cost of treatment (18). These adverse effects have prompted researchers to investigate the outcomes of the combination of gonadotropins with other drugs.

The investigators observed that LTZ is an effective drug for improved follicle recruitment in ovulatory patients with unexplained infertility, lacking the adverse influences on the endometrium and cervical mucus with the treatment of CC (19). And also, it was stated a significant increase by the number of ≥18 mm follicles, early LH elevation rates, required dose of gonadotropins, pregnancy and live birth rates, when LTZ-rFSH combination was used for OI in patients with a prior history of inadequate response to gonadotropin stimulation (20). In the present study, we found that co-treatment of LTZ plus rFSH significantly reduces the gonadotropin dose required and the number of days of stimulation. In numerous studies, it was observed that LTZ reduced the FSH dose required in between 35-55% (16,21,22). In our study, LTZ reduced the rFSH dose required 52.1%. This result indicates that the combined use of LTZ with gonadotropins significantly reduced the cost of treatment. This finding is crucial both in increasing cost-effectiveness and in reducing healthcare costs, especially in developing countries.

Endometrial thickness has shown to be associated with the success of fertility treatment, and the frequently cut-off value of 7 mm was associated with a lower chance of pregnancy (23). The high ovulation and low pregnancy rates of CC have been associated with the pre-dominant anti-estrogenic effect of CC on the endometrium, which ends in long-lasting estrogen receptor depletion (24). In contrast, LTZ does not bind to estrogen receptors and do not cause estrogen receptor depletion (25). Also, the reduction of plasma levels of estradiol (by inhibiting aromatase) upregulates the estrogen receptors in the endometrium (26). This up-regulation results in accelerated endometrial growth once estrogen secretion is returned after the clearance of LTZ (25). In a study by Yun et al., endometrial thickness at the day of hCG administration was significantly higher in the LTZ-Gn group than the CC-Gn group (27). In a study conducted by Noriega-Portella et al., the combined use of LTZ with rFSH resulted in a comparable endometrial thickness on the day of hCG administration compared with rFSH-alone (8.5 mm and 8.9 mm, respectively) (22). In the same study, the pregnancy rate in the LTZ-rFSH group and rFSH alone group was similar (23.6% and 17.9%, respectively, p>0.05). In our research, the endometrial layer in the rFSH group was slightly thicker than in the LTZ-rFSH group (9.2 and 8.7, respectively), but this difference was not statistically significant (p>0.05). The mean endometrial thickness in both groups was within the adequate levels for implantation. We achieved similar pregnancy rates as 17.0% per cycle in the LTZ co-treatment group and 15% per cycle in the rFSH alone group (p>0.05).

Most researchers agree that developing one follicle in OI protocols ended in higher pregnancy and live birth rates (1). Therefore, the purpose of OI in IUI cycles should be one stimulated follicle growth. In our study, there was no difference in the number of ≥18 mm follicles between the LTZ co-treatment group and the rFSH-alone group (1.6 and 1.6, respectively). Also, one mature follicle growth was the most common result in both groups. Gonadotropins are associated with a definite risk for OHSS (13). The combined use of LTZ with rFSH reduces the risk of OHSS (16). In our study, no OHSS cases were seen in both groups. We think that the reason for the absence of OHSS cases in the rFSH alone group is due to the lower mean dose of rFSH with similar clinical pregnancy rates compared to other studies (28).

Another complication related to the use of gonadotropin is multiple pregnancies. When using rFSH alone in IUI cycles, up to 30% of pregnancies are associated with multiple gestations (29). Numerous studies have reported that LTZ reduces multiple pregnancy rates both when used alone and in combination with gonadotropins (5,16). In our study, while multiple pregnancies were not seen in the LTZ-rFSH group, three (5.1%) multiple pregnancies occurred in the rFSH alone group. The reason for the multiple pregnancy rate in the rFSH alone group to be lower than the expected rate can be explained by the low gonadotropin dose administered and our strict cancellation policy. Couples were advised to

cancel a cycle if four or more dominant follicles were observed.

In a study presented in 2005, the incidence of locomotor malformations and cardiac anomalies was higher in the LTZ group than in the control group (30). This result has raised concerns about LTZ use. Later, in many studies, the association between LTZ use and the fetal anomaly was investigated, but no association has been found (31). This finding can be explained by the short half-life of LTZ, providing its complete elimination before the implantation (16). In our study, no fetal anomaly was found in either group.

After the treatment of the groups, we found a live birth rate of 12.8% per cycle for the LTZ-rFSH group versus 8.5% per cycle for the rFSH alone group (p>0.05), which is comparable to the one reported by Noriega-Portella et al. (22).

The strength of this study is that all demographic variables and laboratory values of the treatment groups were similar. Another strength is that pregnancy and neonatal outcomes were examined.

The main limitations of this study are related to its retrospective nature and low sample size. Also, it is not specified whether couples have a history of infertility treatment.

In conclusion, the combined use of LTZ with rFSH resulted in a lower required dose of rFSH, a similar and acceptable endometrial thickness at the day of hCG administration, and a similar pregnancy rate compared with rFSH alone.

Conflicts of interest statement: The authors declare that there is no conflict of interest.

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