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Letrozole versus gonadotropins for ovulation induction in patients with endometriosis: a prospective randomized trial

Endometriozisli hastalarda ovulasyon indüksiyonu ajanı olarak letrozol ve gonadotropinlerin karşılaştırılması: prospektif randomize çalışma

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Abstract

Purpose: This study aimed to compare the effects of letrozole and gonadotropins for ovulation induction in infertile patients with stage 1-2 endometriosis.

Materials and methods: Twenty patients who underwent diagnostic laparoscopy and histologically diagnosed stage 1-2 endometriosis were included in this prospective randomized study. Patients who planned to continue with timed sexual intercourse were randomized into two treatment groups including letrozole (n=10) or gonadotropins (n=10) for minimum three and maximum five treatment cycles.

Results: Ovulation occurred in 37/45 cycles (82.2%) in the letrozole group and 32/37 cycles (86.4%) in the gonadotropin group, without statistically significant difference (p=0.590). Total number of follicles was significantly higher in gonadotropin group on the day of hCG administration (2.33±0.71 vs. 3.05±0.91, p<0.001). Clinical pregnancy rates both per completed cycles and per patients were similar between two groups (8.1% vs. 9.4%, p=0.850 and 30% vs. 30%, p=1.000; respectively).

Conclusions: Letrozole is well tolerated and cost effective ovulation induction agent in patients with endometriosis and effects of letrozole for ovulation induction were comparable to gonadotropins.

Key words: Letrozole, gonadotropin, endometriosis.

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Özet

Amaç: Bu çalışmada letrozol ve gonadotropinlerin evre 1-2 endometriozisli infertil hastalarda ovülasyon indüksiyonu üzerine etkilerinin karşılaştırılması amaçlanmıştır.

Gereç ve yöntem: Prospektif randomize olarak dizayn edilen çalışmaya tanısal laparoskopi yapılan ve histolojik olarak tanı konulan evre 1-2 endometriozisli 20 hasta dahil edildi. Zamanlanmış cinsel ilişki ile devam etmeyi planlayan hastalar, en az üç en fazla beş ovulasyon indüksiyonu döngüsü için letrozol (n=10) veya gonadotropinler (n=10) olmak üzere iki tedavi grubuna ardışık olarak randomize edildi.

Bulgular: Ovulasyon, letrozol grubunda %82,2 (37/45 siklus) ve gonadotropin grubunda %86,4 (32/37 siklus) oranlarında gerçekleşti. İki grup arasında ovulasyon oranları istatistiksel olarak benzerdi (p=0,590). hCG uygulamasının yapıldığı gün gonadotropin grubunda toplam folikül sayısı anlamlı olarak yüksekti (2,33±0,71 ve 3,05±0,91, p<0,001). Klinik gebelik oranları hem tamamlanmış siklus başına hem de hasta başına iki grup arasında benzerdi (sırasıyla siklus başına %8,1 ve %9,4 p=0,850 ve hasta başına %30 ve%30, p=1,000).

Sonuç: Letrozol iyi tolere edilebilen bir ovulasyon indüksiyonu ajanıdır. Evre 1-2 endometriozisli hastalarda letrozolün ovülasyon indüksiyonu üzerindeki etkileri gonadotropinlerle karşılaştırılabilir bulunmuştur.

Anahtar kelimeler: Letrozol, gonadotropin, endometriozis.

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Introduction

Endometriosis is defined as presence of endometrial tissue outside the uterine cavity and is found predominately attached to sites within the peritoneal cavity [1]. The gold standard test to diagnose endometriosis is the direct visualisation of classical or subtle lesions at laparoscopy or laparotomy [2]. It affects approximately 10% of women, with peak incidence between 30 and 45 years of age [3, 4]. Although women may be asymptomatic, most women typically present with pelvic pain, infertility or an adnexal mass [5]. Infertility is associated with this condition and in severe cases is usually due to damage to the tubes and ovaries by inflammation and scar tissue. Distorted pelvic anatomy, altered peritoneal function, altered hormonal and cell mediated function, endocrine and/or ovulatory abnormalities, impaired implantation, oocyte and embryo quality and abnormal uterotubal transport are all mechanisms that have been proved to decrease fecundity in women with endometriosis [5]. Current treatments available for endometriosis include surgery and medical therapy, or both [6]. Infertility medications are specifically used for ovulation induction or for controlled ovarian hyperstimulation with assisted reproductive technology [5, 7].

Letrozole is used for the treatment of endometriosis by suppressing estrogen production locally and systematically [8]. Aromatase inhibitors (AIs) are a promising therapeutic option that may be helpful for the management of endometriosis-associated pain in combination therapy with progestins [9]. Letrozole is also used for ovarian stimulation by blocking estrogen production by inhibiting aromatization would release the hypothalamic–pituitary axis from estrogenic negative feedback [10]. Third-generation AIs, especially letrozole, have challenged clomiphene citrate as an ovulation-induction agent in patients with polycystic ovary syndrome and in cases of unexplained infertility. However, few studies are available regarding the use of AIs to treat endometriosis-associated infertility [11]. Moreover, gonadotropins are associated with higher risk for ovarian hyperstimulation syndrome and multipl gestations [12].

There are few studies have yet compared the effects of letrozole and gonadotropins in infertile patients with endometriosis. The aim of this prospective randomized trial is to compare the efficacy of letrozole to gonadotropins for ovulation induction in infertile women with endometriosis.

Materials and methods

Ethical Committee and Institutional Review Board approval was obtained from Erciyes University Faculty of Medicine, where the study was conducted. Written informed consents were taken from all participants.

This is a prospective randomized trial that included twenty couples in which the women were 20-35 years old and who sought care for unexplained infertility accepted in our institution from June 2007 to June 2009. All couples had a standard infertility evaluation that included a semen analysis, evaluation of tubal patency either by hysterosalpingogram (HSG) or laparoscopy, and a baseline transvaginal ultrasonogram. A baseline hormonal profile that included FSH, LH, TSH, and PRL in the early follicular phase was measured. All men had to have a normal semen analysis according to World Health Organization (WHO) criteria [13]. Midluteal phase serum progesteron was at least 5 ng/mL. Couples with any type of endocrine abnormalities were excluded from the study. In addition women were excluded if they had early follicular, day 3 FSH levels exceeding 12 IU/L. Among 400 women 35 were diagnosed unexplained infertility and underwent diagnostic laparoscopy. 20 of them were laparoscopic diagnosed stage 1-2 endometriosis (Figure 1). American Society for Reproductive Medicine classification of endometriosis scoring system was used for staging the endometriosis [14]. Biopsies were taken from the suspicious areas. Histopathological confirmation of the laparoscopic impression was performed for the diagnosis of endometriosis in all patients.

Patients who were diagnosed stage 1-2 endometriosis and were planned to continue with timed sexual intercourse were consecutively randomized into two treatment groups for minimum 3 and maximum 5 treatment cycles. Patients in group 1 received a daily dose of letrozole (Femara; Novartis, Basel, Switzerland) orally 2.5 mg on days 3-7 of their cycle. Patients in group 2 received recombinant FSH (Gonal-F; Sereno, Bari, Italy or Puregon; Schering Plough, Oss, Netherlands) beginning

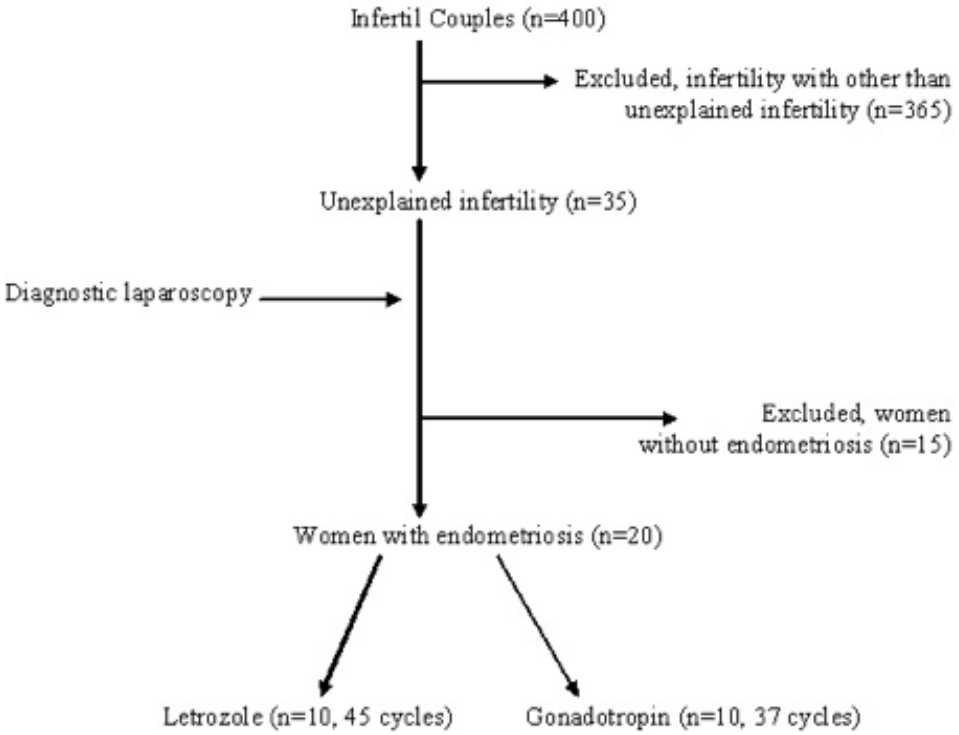

Figure 1. Flowchart of the study protocol.

on day 3 of their menstrual cycle. The starting dose of gonadotropins was 75 IU every day and was continued according to the response of ovarian follicles. All patients underwent a baseline ultrasonographic examination on day 3 of the menstrual cycle and subsequently on day 10. Thereafter, patients had serial sonographic evaluations according to the discretion of the examiner. When the mean diameter of at least one follicle had reached 18 mm, an IM injection of 10,000 IU of hCG (Pregnyl; Schering Plough, Oss, Netherlands) was administered to trigger ovulation. E2 levels on the day of hCG administration was measured in both groups. The endometrial thickness was measured the same day at its greatest diameter perpendicular to the midsagittal plane at the fundal region of the uterus. Then timed sexual intercourse was proposed 36 hours after hCG injection. Serum hCG was determined 1 week later in the absence of menstruation. Fetal cardiac pulse was determined by ultrasonography at 6-7 weeks of gestation for diagnosis of clinical pregnancy.

For statistical analysis a commercially available statistical package SPSS version 13.0 (SPSS, Chicago, IL) was used. Means were analyzed using a Student's t-test. Otherwise a Mann Whitney U test was used. To evaluate differences between proportions, Chi-square test was used. Results are expressed as mean ± SD unless otherwise indicated. A *p* value less than 0.05 was considered statistically significant.

Results

Comparison of the characteristics in the two treatment groups are shown in Table I. There were no differences between the two groups in age, body mass index (BMI), duration of infertility, day 3 FSH, LH, E2, TSH, PRL, free testosteron, and day 21 progesteron levels.

Total number of follicles >14 mm and >18 mm were significantly higher in gonadotropin group than letrozole group on the day of hCG administration ($p<0.001$ and $p=0.022$, respectively). There was no statistically significant difference in pretreatment endometrial thickness between the two groups ($p=0.053$). The endometrial thickness on the day of hCG administration in letrozole group was observed significantly thinner compared to the gonadotropin group (8.09±1.29 mm vs. 9.53±1.73 mm, $p<0.001$). Ovulation occurred

in 37/45 cycles (82.2%) in letrozole group and 32/37 cycles (86.4%) in gonadotropin group without significant difference between both groups (p=0.590). Serum E2 concentrations on the day of hCG administration were significantly higher in gonadotropin group than letrozole group (156.09±116.80 pg/ml vs. 303.68±181.24 pg/ml, p<0.001). Clinical pregnancy rates were similar per completed cycles were 3/45 (8.1%) in letrozole group and 3/37 (9.4%) in gonadotropin group (p=0.850). Clinical pregnancy rates per patients were also similar between the groups (30% vs. 30%, p=1.000). Clinical pregnancy was defined as determining the fetal heart beat at 6- 7 weeks gestational age. There was only one first trimester abortion in gonadotropin group. There was no difference in take home baby rate between two groups (30% vs. 20%, p=0.601). There were no twin pregnancies in both groups (Table II). None of the treatment cycles resulted in moderate or severe ovarian hyperstimulation syndrome (OHSS).

Table I. Comparison of characteristics in letrozole and gonadotropin groups.

	Group 1 (Letrozole group, n=10)	Group 2 (Gonadotropin group, n=10)	*p*
Number of cycles	45	37	0.593
Age (y)	26±3.43	28.3±4.47	0.212
BMI (kg/m^2)	22.66±2.16	23.8±3.23	0.360
Duration of infertility (y)	5.5±1.90	7.7±4.19	0.144
Day 3 FSH (mIU/ml)	6.26±1.68	5.99±1.57	0.712
Day 3 LH (mIU/ml)	3.94±0.74	3.19±1.26	0.124
Day 3 E_2 (pg/ml)	51.72±15.27	42±10.16	0.142
Day 3 TSH (µg/ml)	1.99±0.48	1.60±0.57	0.114
Day 3 PRL (ng/ml)	8.60±2,03	10.65±3.64	0.142
Day 3 free testesteron (pg/ml)	1.77±0.81	1.81±0.56	0.913
Day 21 Progesteron (ng/ml)	10.41±3.19	13.77±8.34	0.312

BMI= body mass index; FSH= follicle-stimulating hormone; LH= luteinizing hormone; E2= estradiol; TSH= thyroid stimulating hormone; PRL= Prolactin.

Table II. Outcomes in letrozole and gonadotropin groups.

	Group 1 (Letrozole group, n=10)	Group 2 (Gonadotropin group, n=10)	*p*
Total number of follicles	2.33±0.71	3.05±0.91	**<0.001**
Number of follicles > 14 mm on day of hCG injection	1.27±0.54	1.81±0.66	**<0.001**
Number of follicles > 18 mm on day of hCG injection	1.06±0.25	1.24±0.43	**0.022**
Pretreatment endometrial thickness	3.75±0.79	3.91±0.65	0.053
Endometrial thickness on day of hCG injection	8.09±1.29	9.53±1.73	**<0.001**
E_2 levels on day of hCG injection	156.09±116.80	303.68±181.24	**<0.001**
Ovulation/ cycle	37/45 (82.2%)	32/37 (86.4%)	0.590
Pregnancy rate per cycle	3 (8.1%)	3 (9.4%)	0.850
Pregnancy rate per patient	3 (30%)	3 (30%)	1.000
Take home baby rate	3 (30%)	2 (%20)	0.601

hCG= human chorionic gonadotropin; E2= estradiol.

Discussion

In the present study, patients with stage 1-2 endometriosis who have not any endocrinological and anatomic pathology were evaluated. Histopathological confirmation of the laparoscopic impression was performed for the diagnosis of endometriosis. Then, patients were randomized into letrozole and gonadotropin treatment groups consecutively for ovulation induction. Several studies report success with superovulation (SO) and intrauterine insemination (IUI) in the treatment of endometriosis associated infertility.

Endometriosis may affect fertility by various mechanisms, including distortion of pelvic anatomy from adhesions, intraperitoneal inflammation, which can decrease oocyte quality and/or oocyte-sperm interactions, abnormal tubal transport, and implantation defects [15]. There are inconsistent results in the literature for assisted reproductive technology (ART) results in women with endometriosis. GnRH agonists, progestins, danazol, gestrinone, ovulation suppressing agents (combined hormonal contraceptive preparations, dienogest), GnRH antagonists, anti-inflammatory agents, aromatase inhibitors, the levonorgestrel intrauterine device, selective progesterone receptor modulators are all on-label and off-label drugs used in the treatment of endometriosis [16]. Both medical and surgical treatments (presacral neurectomy, endometrioma excision) for pain associated with endometriosis are effective [17]. Whereas medical therapy is effective for relieving pain associated with endometriosis, there is no evidence that medical treatment of endometriosis improves fertility. In actuality, fertility is essentially eliminated during treatment because all medical treatments for endometriosis inhibit ovulation [5]. According to the recent literature, there is insufficient evidence to indicate that resection of endometriomas prior to IVF improves outcomes. In women with stage 3-4 endometriosis-associated infertility, conservative surgical therapy with laparoscopy or possible laparotomy (resection or ablation, rather than drainage) may be beneficial. For women with stage 3-4 endometriosis who fail to conceive following conservative surgery or because of advancing reproductive age, IVF-ET is an effective alternative. The benefit of laparoscopic treatment of minimal and mild endometriosis is insufficient to recommend laparoscopy solely to increase the likelihood of pregnancy. In younger women (<35 years) with stage 1-2 endometriosis associated infertility, expectant management or SO/IUI (superovulation and IUI) can be considered as first line therapy [5, 18].

In stage 1-2 endometriosis, laparoscopic ablation of endometriotic implants has been associated with a small but significant improvement in live birth rates. Two randomized controlled studies [19-20] have evaluated effectiveness of laparoscopic surgery for stage 1-2 endometriosis associated with infertility, one of which showed benefit.

There are studies in the literature suggesting that SO/IUI may be a viable treatment option for women who had a surgical or histologic diagnosis of stage 1-2 endometriosis before further treatment options [21-24].

The potential role of aromatase inhibitors in the treatment of endometriosis associated symptoms, mainly pain and infertility is an important issue. The early administration of letrozole in the follicular phase induces ovulation by releasing the hypothalamic–pituitary axis from estrogen negative feedback, thus increasing FSH secretion, stimulating ovarian follicular development. In addition, it increases follicular sensitivity to FSH by the accumulation of intraovarian androgens [25]. Studies have shown that letrozole may be superior to CC when comparing side effects, ovulation, and pregnancy rate in a general infertile population [26-27]. Therefore letrozole have challenged clomiphene citrate as an ovulation induction agent in patients with polycystic ovary syndrome as well as unexplained infertility. Among anovulatory patients with PCOS, letrozole has also been shown to induce ovulation and attain a 25% pregnancy rate [28]. However few studies are available with regard to letrozole use for ovulation induction in women with endometriosis associated infertility. There are two randomized controlled studies in the literature using letrozole as an ovulation induction agent in women with endometriosis associated infertility in non-IVF cycles. Alborzi et al. [29] evaluated 144 women using letrozole 2.5 mg/day vs. triptorelin 3.75 mg IM every month vs. no medication for two months after laparoscopic surgery with a 12 months follow-up. They found no differences

among the three groups with regard to pregnancy rate as well as disease recurrence rate. Abu Hashim et al. [30] compared letrozole/IUI and CC/IUI in stage 1-2 endometriosis with no pregnancy 6-12 months after laparoscopy. Their results suggested no significant differences between both groups for clinical pregnancy rate, cumulative pregnancy rate, and miscarriage or live birth rates. In the present study we compared the effects of letrozole and gonadotropins for ovulation induction in infertile patients with stage 1-2 endometriosis. A significant decrease in endometrial thickness on the day of hCG administration was observed in the letrozole group. However, it was adequate for implantation. Studies showed that letrozole is associated with a thinner endometrium [31]. This might be due to low dose E2 levels. In the present study, letrozole was associated with fewer developing and mature follicles; however, no statistically significant difference was observed regarding ovulation or clinical pregnancy rates between the two groups. Ovulation occurred in 37/45 cycles (82.2%) in letrozole group, which is comparable to that reported by Badawy et al. [32] who had an ovulatory rate of 62% for letrozole cycles. In other trials, Mitwally and Casper [33] had ovulatory rate of 75%, Al- Omari et al. [34] had an ovulatory rate of 87.5%, whereas Elnashar et al. [28] reported an ovulation rate of 54.6%. Pregnancy per cycle was achieved in 8.1% in group 1, which is comparable to 12.2% reported by Badawy et al. [32]; however, it is less than that reported by other investigators (25% and 27%) [28, 34]. The miscarriage rate was also similar in both of our groups.

To our knowledge, no studies have yet compared the effects of letrozole monotherapy to gonadotropins in patients with endometriosis. Only one study compared pregnancy rates for letrozole and gonadotropins in individuals who failed to conceive with clomiphene citrate in patients with PCOS associated anovulation, unexplained infertility, or mild male factor infertility [27]. In these individuals, side effects, average pregnancy rates per cycle for letrozole and gonadotropin treatments were equivalent. In our study pregnancy rates were similar. Additionally, because of low dose regimen there was not any multiple pregnancy and OHSS in gonadotropin.

Letrozole has significantly lower cost than gonadotropin for ovulation induction. However, data on cost per pregnancy is not definite when comparing letrozole to gonadotropins for ovulation induction. The decreased risk of multiple gestations associated with ovulation induction by letrozole when compared to treatment with gonadotropins has also superiority. In our study, medication costs with letrozole should be significantly less than that of gonadotropins per month of stimulation. Letrozole requires less ultrasound monitoring and possibly less blood assay measurements per cycle of treatment when compared to gonadotropins, which should also reduce treatment costs.

In conclusion, our findings suggest that letrozole and gonadotropins have comparable effect for ovulation induction and achieving pregnancy in patients with histologically documented endometriosis. Additionally, letrozole is well tolerated and cost effective treatment comparing gonadotropins. Because letrozole is taken orally, requires less monitoring than gonadotropins, and has less side effects, it may represent a reasonable alternative to gonadotropins. While prospective design may provide advantages, small sample size is a limitation. Further prospective studies with larger sample size are needed in the field.

Conflict of interest: No conflict of interest was declared by the authors.

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