Comparison of Gonadotropin with Gonadotropin and Letrozole Combination in Infertile Women with Biopsy - Proven Endometriosis Undergoing Intracytoplasmic Sperm Injection

Burak TANIR[1], Mehmet SERDAR KÜTÜK[1], Mehmet DOLANBAY[1], Mahmut Tuncay ÖZGÜN[1], Semih ULUDAĞ[1], Ercan AYGEN[1], Yılmaz ŞAHİN[1]

Kayseri, Turkey

OBJECTIVE: To compare the result of intracytoplasmic sperm injection cycles using gonadotrophins with those of using gonadotrophins combined with letrozole in infertile woman with biopsy-proven endometriosis.

STUDY DESIGN: This prospective randomized study was performed at the department of Obstetrics and Gynecology Reproductive Center, in Erciyes University. Thirty- three women undergoing intracytoplasmic sperm injection (ICSI) with gonadotropin or combination of gonadotropin with letrozole were accepted. The patients were grouped as: gonadotropin group (Group 1), and gonadotropin plus letrozole (Group 2). Total and clinical pregnancy ratios, length of cycles, and doses of gonadotropin used were compared.

RESULTS: Total doses of gonadotrophins used in group 1, and group 2 were 2700 (1800- 3600) IU and 2100 (1575- 3475) IU, respectively. Total dose of gonadotropin used in group 2 was found to be lower than that of group one and this difference was statistically significant (p= 0.002). Stimulation times in group 1 and 2 were 10 (9- 12) day, and (7- 12) day, respectively, and the difference was statistically significant (p=0.048). Number of the retrieved oocytes were higher in group 2 than Group 1(p=0.027). There was no statistically significant difference between groups with regard to numbers of embryos, total and clinical pregnancy ratio.

CONCLUSIONS: Letrozole has no effect on the results of ICSI success in infertile women with biopsy proven- endometriosis. However, it reduces the gonadotropin dose used, stimulation time and, cost of the therapy.

Key Words: Infertility, Endometriosis, ICSI, Letrozole, Gonadotropin

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Introduction

Endometriosis is a benign disease affecting approximately 10% of reproductive age woman.[1] Endometriosis is associated with variety of clinical condition, such as, dysmenorrhea, and dyspareunia, chronic pelvic pain, and it plays an enigmatic role in the causation of infertility. Long list of theory have been proposed in an attempt to explain the subfertility associated with endometriosis. Briefly, this hypothesis can be summarized as: adhesion formation, deterioration of follicular growth, decreased fertilization, immunological derangement, and insufficient implantation. There are also fundamental abnormal changes within the eutopic endometrium of women with endometriosis compared to normal endometrium of women without endometriosis. Eutopic endometrium shows enhanced ability of proliferation, implantation and angiogenesis, and greater probability of escaping the unfavorable conditions of the ectopic environment.[2]

Although association between severe endometriosis and infertility can be explained by the presence of severe adhesions, and anatomical distortion, relationship between mild degree of endometriosis and subfertility remains obscure.[3] It has been showed by Nobel et al. that endometriotic lesions have an ability to synthesis of estrogen from androstenedione by way of aromatization. Estrone that is synthesized by this mechanism is converted to more potent estradiole (E2) and inhibits follicle stimulating hormone (FSH).[4] After the discovering of this mechanism, aromatase enzyme that is responsible for the conversion of androstenedione to estrone has been the target of new treatment modalities, and specific inhibitors such as letro-

[1] *Erciyes University Faculty of Medicine Department of Obstetrics and Gynecology, Kayseri*

Address of Correspondence: *Mehmet Dolanbay*
Erciyes University, Faculty of Medicine
Department of Obstetrics and
Gynecology Kayseri, Turkey
mdolanbay@erciyes.edu.tr

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zole have been studied regarding their effectiveness for the treatment of infertility secondary to endometriosis.

Aromatase is a member of the P450-hemoprotein enzyme complex family catalyzing the rate limiting step of the conversion of androstenedione to estrone, and testosterone to E2, respectively.[5] Being a terminal step in the synthesis of estrogen, aromatization is thought to be a good target for the selective inhibition of estrogenesis.

The aim of the present study is therefore to compare the result of gonadotropin stimulated intracytoplasmic sperm injection (ICSI) cycles and gonadotropin plus letrozole stimulated cycles and thus assess the presumptive contribution of aromatase inhibitors on ICSI outcome in controlled ovarian hyperstimulation in patients with biopsy-proven endometriosis.

Material and Method

This study was conducted at Erciyes University, department of reproductive endocrinology and infertility between February 2009 and June 2011. The entire woman enrolled in the study was examined before treatment. Tubal patency and anatomical structure were examined with hysterosalpingography. During the early follicular phase, transvaginal ultrasonography was performed to evaluate antral follicle number. FSH, luteinizing hormone (LH), estradiole (E2), thyroid-stimulating hormone (TSH), prolactin levels were assayed at third day of cycle. Women who have anatomic and endocrinological problems were excluded from the study. Male factor was evaluated with semen analysis and patients with abnormal results defined by World Health Organization (WHO) criteria were excluded from the study. Forty seven infertile women who were diagnosed as unexplained infertility and whose symptoms and ultrasonographic finding suggesting endometriosis and/or endometrioma were undergone laparoscopy and lesions suspicious for endometriosis were sampled for pathological examination. After the evaluation of the abdomino-pelvic structures and peritoneal surface, adhesiolysis by sharp dissection was performed to fully mobilize the ovaries and other pelvic structures. All the peritoneal lesions were excised, cystectomy was performed for all endometriomas and the tissues were sent for pathologic examination. 33 patients were included in the study only if endometriosis was confirmed histologically. Thirty patients undergone at least two cycles of ovulation induction and intrauterine insemination before laparoscopic procedure and three patients bilateral hydosalpinx demonstrated with laparoscopy whose HSG examination were normal two years ego. Thirty three patients were elected for ICSI. The severity of the disease was categorized according to the American Fertility Society classification.[3]

Women with biopsy-proven endometriosis were randomized to gonadotropin (Group 1), and gonadotropin plus letrozole (Group 2) groups by means of selecting an envelope by the patient including two different colored cards representing two study groups. The ICSI protocol used pituitary down regulation using the gonadotropin releasing hormone agonist (GnRH- a) leuprolide acetate (Lucrin 10 IU/day, Abbott) commencing in the mid- luteal phase of the preceding cycle. After the confirmation of pituitary down- regulation, recombinant follicle stimulating hormone (r-FSH, Gonal-F, Merc Serono) was initiated at the day 3 of the cycle to both groups the doses of which were based on the patient's ages, weights, baseline FSH, and E2 levels, antral follicles numbers, and their response to previous stimulation. In group 2, letrozole (Femara 2,5mg, Novartis) 2,5 mg/day was started concomitantly with r- FSH at day 3 and continued for 5 days consecutively.

Cycles were monitored by serial transvaginal ultrasonography, and E2 levels. When at least three follicles of 18 mm or greater were noted on the serial ultrasound monitoring, chorionic gonadotropin alpha (Ovitrelle 250mcg, Serono) was administered and patients were scheduled for oocyte retrieval after 36 hours. After the 72 hours of oocyte retrieval, ultrasound- guided embryo transfers (ET) were performed by the two operators (E.A and Y.S).

Luteal phase support was provided with vaginally applicated micronised progesterone (Crinone vaginal gel, Serono). Quantitative estimation of serum beta- human chorionic gonadotropin (B- hCG) was performed 12 days after ET. If it gives positive results, repeat test was performed after two days and the escalation of titers were evaluated. Patients with normally escalating B- hCG titers were scheduled for transvaginal ultrasound examination after 15 days in order to evaluate the presence of gestational sac and fetal cardiac activity. Clinical pregnancy was defined as the presences of gestational sac and fetal cardiac activity.

All data sets were subjected to normality tests using the Kolmogorov-Smirnov method and data were reported as either mean ± standard deviation (mean ± SD) (for normally distributed data and proportions), or as median with minumum and maximum (for skewed data). Comparison of variables between the two groups was made using the Mann-Whitney U test for skewed data, Student's t test for normally distributed data and Chi-square test for proportions. A two tailed p value of <0.05 was considered statistically significant. Data were analyzed by Statistical package for the social scienses (SPSS) 19.0. (IBM Corporation, USA).

Results

The mean age of the study population was 29.1±3.36. The body mass index of the population was 23.3±2.74. The mean duration of infertility was 7.14±3.79 years.

The patients in group1 were older than group 2 (30.2±3.06vs 29.7±3.27, p>0.05) There were no statistically significant difference between Body Mass Index (BMI), duration of infertility, basal FSH and E2 levels (p> 0.05). The day 3 antral follicles number were median 12.50 (min 7- max 22) and median 14.00 (min 7- max 22) for group 1 and group 2, respectively. No statistically significant difference was found between pre-induction antral follicles numbers (p>0.05). Patients characteristic and basal E2, FSH levels, and antral follicles numbers in groups are shown in table 1.

Table 1: Comparasion of patients characteristic and basal E2, FSH levels, and antral follicules numbers

	Groups		P
	Group 1 n=18	Group 2 n=15	
Age (years) mean±SD	30.22±3.06	29.67±3.27	0.127
BMI (kg/m²) mean±SD	23.09±2.71	23.55±2.84	0.642
Duration of infertility (years) mean±SD	6.47±3.37	7.93±4.22	0.277
Basal FSH (mIU/ ml) mean±SD	6.90±2.45	5.99±1.70	0.231
Basal E2 (pg/ml) Median (Min-Max)	70.56 (18.55-89.25)	50.40 (20.51-120.33)	0.108
Number of Antral foliculles Median (Min-Max)	12.50 (7-22)	14.00 (7-22)	0.166
Endometrial thickness (mm)	10.62±1.54	10.11±1.95	0.401

BMI: Body Mass Index, FSH: Follicules stimulating hormone, E2: Estradiol, SD: Standart deviation

Oocyte retrieval was cancelled in one patient in group 1 who was unresponsive to stimulation. Total dose of r-FSH for 18 patients-cycles in group 1 and 15 patients-cycles in group 2 were median 2700 (min 1800- max 3600) and median 2100 (min 1575- max 3475) IU, respectively. Total r-FSH dose for group 2 was significantly lower than that of group 1 (p= 0.002). Similarly, length of stimulation was shorter in group 2 than group 1 with statistical significance (p=0.048). Number of the retrieved oocyte were higher in group 2 (median [7min 0-max 18]) than Group 1 (median 12 [min 0 -max 19]) (p=0.027). There were no statistically significant difference regarding mature oocyte follicles between groups (p> 0.05). There was no statistically significant difference regarding endometrial thickness at the day of b-hCG administration between groups (p>0.05)

Fertilization ratio for the groups was found to be 87.5%, and 100%, respectively (p>0.05). One patient from each group did not developed embryo. Mature oocyte number were median 6 (min 0-max 14) and median 8 (min 1-max 21), respectively. There were no statistically significant difference between groups (p>0.05). Endometrial thickness at the day of hCG administration were similar in the two groups (p>0.05). In addition, no statistically significant differences were also found between number of available embryos on Day 3 (median 3.50 [min 0-max 10]) versus [median 5 (min 0-max 19)], (p>0.05). As main outcome of study, there were no statistically significant difference between pregnancy ratio, and clinically pregnancy rate per cycle initiated. Comparison of groups with respect to cycles characteristics, and main outcomes were shown in table 2.

Table 2: Comparison of groups with respect to total doses of r-FSH used, the length of stimulation, oocytes retrieved, and the other treatment outcome

	Groups		P
	Group 1 n=18 Median (Min-Max)	Group 2 n=15 Median (Min-Max)	
Total dose of r-FSH (IU)	2700 (1800-3600)	2100 (1575-3475)	0.002
Length of stimulation (day)	10 (9-12)	9 (7-12)	0.048
Oocytes retrieved (n)	7 (0-18)	12 (1-23)	0.027
Mature oocytes (n)	6 (0-14)	8 (1-21)	0.108
Number of available embryos on Day 3 (n)	3.50(0-10)	5(0-19)	0.381
Numberoftransferredembriyos (n)	1.40 (1-2)	1.43 (1-2)	0.622
Pregnancy ratio [(%)]	7(38.9)	5(33.3)	1.00
Clinical pregnancy ratio [(%)]	5(27.8)	3(20)	0.911

r-FSH: Recombinant follicules stimulating hormone

Subanalysis of groups based on the severity of endometriosis (grade 1- 2/ grade 3-4) showed that like the main groups, dose of r-FSH and length of stimulation was lower in letrozole group and difference was statistically significant (p<0.05). The other parameters were found to be similar in the treatment groups. The comparison of data of patients with grade 1-2 endometriosis and grade 3-4 endometriosis are shown in table 3, and 4 respectively.

Table 3: Comparasion of cycle parameters of patients with grade 1 and 2 endometriosis between group1 and group 2

	Groups		P
	Group 1 Grade 1- 2 n=8	Group 2 Grade 1-2 n=7	
r-FSH dose (IU)	2850 (2200-3600)	2025 (1575 2875)	0.029
Length of stimulation (day)	11(9-12)	9 (7-12)	0.152
Oocytes retrieved	11(0-18)	15 (1-23)	0.336
Mature Oocytes	7.50 (0-14)	11(1-21)	0.463
Number of available embryos on Day 3	4 (0-10)	5 (1-19)	0.336
Fertilization ratio [(%)]	7 (87.5)	7 (100)	0.172
Pregnancy ratio [(%)]	4 (50)	3 (42.9)	0.707
Clinical pregnancy ratio [(%)]	3 (37.5)	2 (28.6)	0.674
Endometrial thickness (mm)	10.55 (8-12.50)	9 (8-15)	0.463

Recombinant follicules stimulating hormone (r-FSH), Internationale Unite (IU)

Table 4: Comparasion of cycle parameters of patients with grade 3 and 4 endometriosis between group1 and group 2

	Groups		P
	Group 1 Grade 3- 4 n=10	Group 2 Grade 3-4 n=8	
r-FSH dose (IU)	2662(1800-3600)	2100(1800-3475)	0.043
Length of stimulation (day)	10 (9-12)	9.50 (8-12)	0.237
Oocytes retrieved	6 (0-11)	12 (4-22)	0.120
Mature follicule	5 (0-10)	8 (1-15)	0.101
number of available embryos on Day 3	2.50 (0-8)	4.50 (0-6)	0.829
Fertilization ratio [(%)]	8 (80)	7 (87. 5)	0.172
Pregnancy ratio (%)	3 (30)	2 (25)	0.707
Clinical pregnancy ratio (%)	2 (20)	1 (12.5)	0.674
Endometrial thickness (mm)	10 (9-14.50)	9.80 (8-12.40)	0.408

r-FSH: Recombinant follicules stimulating hormone, SD: Standart deviation

In patients with grade 3-4 endometriosis, like those of grade 1- 2 groups, dose of r-FSH and the length of stimulation were lower in letrozole group. Analysis of data regarding fertilization ratio, oocytes retrieved, embryo formed, mature follicles, total, and clinical pregnancy ratio showed no statistically significant difference between groups. Comparison of data of patients with grade 3 and 4 endometriosis between group 1 and group 2 is shown in table 4 - figure 1.

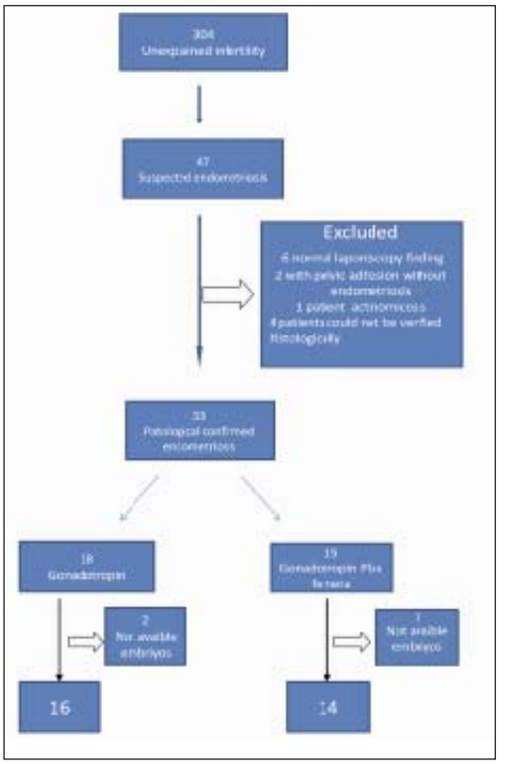

Figure 1: Flow chart trough trial of gonadotropin plus letrozole in ICSI cycles infertilite women with Biopsy - Proven Endometrosis

Discussion

Endometriosis has been suggested as an important factor responsible for decreased success rate of IVF/ICSI, and variety of mechanism by which endometriosis affects IVF outcome had been proposed.[6-8] Up to date, no single theory had been able to account satisfactorily neither the relationship between endometriosis and IVF outcome nor the possible mechanism by which it exerts its effects.

Analysis of our data showed that, baseline demographic parameter, and day 3 E2, FSH levels and antral follicles number similar between groups. The most striking difference between groups was seen in the parameters concerning cost of the cycles, namely dose of r-FSH and length of cycles. Previously, it was shown that, letrozole, by means of decreasing follicular estrogen synthesis, causes elevated FSH secretion and creates hormonal milieu like that of polycystic ovary syndrome and enhance follicular response to r-FSH.[9,10] Moreover, it was shown that elevated levels of androstenedione enhance primate ovarian follicular growth by augmenting the FSH receptor expression on granulosa cells that further contribute to enhancement of ovarian response by letrozole.[11-13] Based on

our results and previous literature, it can be said that letrozole, when combined with r- FSH, decreases the cost of the IVF cycles.

As main outcomes of the study, total and clinical pregnancy rates between groups were similar to each other (%38, 9% versus %33 %, p:1.00 and 27, 8% versus 20%, p: 0.911, respectively). For further analysis, we grouped our patients according to the grade of their endometriosis (Grade 1-2 and Grade 3-4) and, thus, aimed to prevent the bias the degree of endometriosis may have caused. Subgroup analysis showed that in both groups, letrozole significantly reduces r- FSH dose, and length of stimulation. No statistically significant difference was found between the other parameters. In the earlier studies concerning with the possible effect of endometriosis on IVF outcomes, endometriosis was found to be responsible for the lower oocytes retrieved number in patients undergoing laparoscopic oocytes retrieval.[14,15] Our findings supports the recent literature which shows that a replacement of laparoscopic oocytes retrieval with the USG-guided transvaginal approach radically change the success rate of oocytes retrieval and mature follicles number even in patients with high grade endometriosis.[16-18] In addition, negative influence of the cytokines and toxic factors which are supposed to have an adverse effect on ovulation and fertilization is seems to be overcome by way of in vitro fertilization which prevent oocytes and sperms from contacting peritoneal fluid harboring noxious substances.[6-8]

The inferior IVF/ICSI outcomes of endometriosis women may result from decreasing number of retrieved oocytes and affected quality of oocytes/embryos.[19] In our study we tried to assess the possible effect of letrozole on implantation success on ICSI cycles. According to our results, no statistically significant difference found between implantation rate in grade 1-2 and grade 3- 4 groups. It has been previously demonstrated that increased follicular androgen concentration stimulate insulin-like growth factor- 1 (IGF-1), and IGF-2 receptor expression and contribute to the follicular steriodogenesis and maturation.[16,17] Elevated androgen and IGF-1 and IGF-2 concentrations by letrozole may improve oocytes implantation rate by aforementioned mechanism.[20-21] It was also shown that letrozole has no negative effect on endometrial thickness and triple line pattern which is compatible with our results.[22] On the other hand, Bergendal et al. showed no difference between implantation rate in tubal infertility and endometriosis related infertility and added an another dimension to the discussion.[23] Despite the lack of sufficient evidence, it may be speculated that letrozole by way of its effect on granulosa cell receptor may cause improvement in oocytes quality and overcome the deleterious effect of endometriosis on implantation. More recently, it was shown that mice with experimentally induced endometriosis in which the expression of aromatase has been genetically disrupted exhibit significantly smaller endometriotic implants.[24,25] At this point, it was difficult to conclude whether letrozole has a role in improving embryo quality and implantation rate, as well as which mechanism mediates this effect in human. In patients with grade 1-2, and 3-4 endometriosis, total and clinical pregnancy ratio were found to be similar in letrozole and combination groups. From the point of statistical power, the small number of patient who has either biochemical or clinical pregnancy in the subgroups refrained us from drawing definitive conclusion from this analysis.

In our study, we tried to implement stringent inclusion criteria to exclude factors other than endometriosis which could create subfertility and may be the source of potential bias. Besides, in contrast to previous studies including patients who have recurring IVF failure or poor responders, our study population are consist of patients who have not poor prognostic indicator and/or history. Thus we aimed to create optimal study population to ensure us to assess the effect of letrozole in patients with endometriosis undergoing ICSI. However, the major shortcoming of the present pilot study is the sample size which resulted from the stringent inclusion criteria. Furthermore, as far as can be ascertained, this is the first study assessing the effect of letrozole on ICSI outcome in infertile patients with biopsy-proven endometriosis.

In conclusion, it can be said that letrozole when combined with r-FSH in patients with endometriosis, compared to r-FSH induced cycles, shortens the length of stimulation and decrease dose of r-FSH used and thus decreases the cost of therapy. These effects were seen in patients with both grade1- 2 and grade 3-4 endometriosis. To make definitive conclusion regarding letrozole efficiency in IVF/ICSI cycles, this study should be supported by the other randomized study containing larger patient population.

Biyopsi ile Tanısı Doğrulanmış Endometriozisi Olan İnfertil Kadınların İntrasitoplazmik Sperm Enjeksiyon Uygulamalarında Gonadotropin ve Gonadotropin-Letrozol Kombinasyonunun Karşılaştırılması

AMAÇ: Bu çalışmanın amacı biyopsi ile tanısı doğrulanmış endometriozisi olan infertil kadınların intrastoplazmik sperm enjeksiyon uygulamalarında gonadotropin ve gonadotropin-letrozol kombinasyonunun sonuçlarını karşılaştırmaktır.

GEREÇ VE YÖNTEM: Bu prospektif randomize çalışma Erciyes Ünversitesi Obsteri ve Jinekoloji ünitesinde gerçekleştirildi. Çalışmaya, gonadotropin ya da gonadotropin-letrozol kombinasyonu ile intrastoplazmik sperm enjeksiyon siklusu (ICSI) uygulanan 33 hasta kabul edildi. Total ve klinik gebelik oranları, siklus uzunlukları ve kullanılan gonadotropin dozları karşılaştırıldı.

BULGULAR: Kullanılan total gonadotropin dozları gonadotro-

pin grubunda (grup 1) ve letrozol artı gonadotropin grubu (grup 2) için 2700 (1800-3600) IU ve 2100 (1575-3475) IU olarak bulundu. Grup 2'de kullanılan gonadotropin dozu grup 1'den daha az olarak bulundu ve bu istatistiksel olarak anlamlıydı (p=0,002). Grup 1 ve grup 2'de stimülasyon süreleri 10 (9-12) ve 9 (7-12) gün olarak bulundu ve buda istatistiksel olarak anlamlıydı (p=0.048). Toplanan oosit sayısı Grup 1'de Grup 2'ye göre anlamlı olarak daha fazla idi (p=0,027) Embriyo sayıları, total ve klinik gebelik oranları karşılaştırıldığında gruplar arasında istatistiksel olarak anlamlı fark görülmedi.

SONUÇ: Biyopsi ile doğrulanmış endometriozisi olan infertil kadınların ICSI başarısında letrozolun etkisi yoktur. Bununla birlikte letrozol, kullanılan gonadotropin dozunu, stimülasyon süresini ve tedavi maliyetini azaltmaktadır.

Anahtar Kelimeler: İnfertilite, Endometriozis, ICSI, Letrozol, Gonadotropin

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