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Laparoscopic Ovarian Drilling: Is It a Safe Alternative of Gonadotropin Treatment for Second-line Therapy in Patients with Polycystic Ovary Syndrome Resistant to Clomiphene Citrate?

Laparoskopik Ovaryan Drilling: Klomifen Sitrata Dirençli Polikistik Over Sendromu Hastalarında İkinci Basamak Tedavide Gonadotropin Tedavisine Güvenli Bir Alternatif midir?

İpek ESKİYÖRÜK,[a] Rauf MELEKOĞLU,[b] Cihan ÇETİN,[c]
İbrahim Ferhat ÜRÜNSAK,[d] Mehmet Turan ÇETİN[d]

[a]Clinic of Obstetrics and Gynecology, Şanlıurfa Education and Research Hospital, Şanlıurfa, Turkey
[b]Department of Obstetrics and Gynecology, İnönü University Faculty of Medicine, Malatya, Turkey
[c]Department of Obstetrics and Gynecology, Bahçeşehir University Faculty of Medicine, İstanbul, Turkey
[d]Department of Obstetrics and Gynecology, Çukurova University Faculty of Medicine, Adana, Turkey

ABSTRACT

Objective: The objective of this study is to compare the effectiveness and outcomes of laparoscopic ovarian drilling (LOD) and ovulation induction with gonadotropins in polycystic ovary syndrome (PCOS) patients resistant to clomiphene citrate. **Material and Methods:** The medical records of all women admitted to the Infertility Outpatient Clinic of the University of Cukurova School of Medicine, between January 2002 and July 2015, were retrospectively reviewed. A total of 124 women met the study criteria; of these, 33 constituted the LOD group, and 91 the gonadotropin group. **Results:** Age, body mass index, the duration of infertility, basal follicle-stimulating hormone level, and antral follicle count showed no significant differences between groups. Significant reductions in ovarian volume, luteinizing hormone, and total testosterone level were evident at 2 and 6 months after LOD ($p=0.011$, $p<0.001$, and $p=0.002$, respectively). Eight patients in the gonadotropin group (8.7%) developed ovarian hyperstimulation syndrome (OHSS), a complication; no LOD patient developed OHSS. The clinical pregnancy, abortion, and live birth rates were all similar between the two groups. **Conclusion:** We found that pregnancy outcomes were similar in PCOS patients resistant to clomiphene citrate who underwent LOD and exogenous gonadotropin treatment, but the OHSS risk was significantly lower in the LOD group.

Keywords: Ovarian hyperstimulation syndrome; ovulation induction; pregnancy; infertility; laparoscopy

ÖZET

Amaç: Çalışmamızın amacı klomifen sitrata dirençli polikistik over sendromu (PKOS) hastalarında, laparoskopik ovaryen drilling(LOD) ve gonadotropinlerle ovulasyon indüksiyonu tedavilerinin etkinliğini ve sonuçlarını karşılaştırmak. **Gereç ve Yöntemler:** Ocak 2002 ile Temmuz 2015 tarihleri arasında Çukurova Üniversitesi Tıp Fakültesi İnfertilite polikliğine başvuran tüm hastaların tıbbi bilgileri retrospektif olarak incelendi.124 hasta çalışma kriterleni karşıladı; bunlardan 33'ü LOD grubunu, 91'i gonadotropin grubunu oluşturdu. **Bulgular:** Yaş, vücut kütle indeksi, infertilite süresi, bazal follikül stimulan hormon düzeyleri ve antral follikül sayımı açısından gruplar arasında fark saptanmadı. Over hacmi, lüteinizan hormon ve total testosteron düzeylerinde LOD'dan 2 ve 6 ay sonra belirgin azalma saptandı. ($p=0.011$, sırasıyla $p<0.001$, and $p=0.002$) Gonadotropin grubundaki 8 hastada(%8,7), bir komplikasyon olarak değerlendirilen ovaryan hiperstimülasyon sendromu (OHSS) gelişirken, LOD grubunda OHSS oluşmadı. İki grup arasında klinik gebelik, düşük ve canlı doğum oranları benzer saptandı. **Sonuç:** Klomifen sitrat tedavisine dirençli PKOS hastalarında, LOD ve gonadotropin tedavisinin gebelik sonuçlarının benzer, fakat OHSS riskinin LOD grubunda belirgin olarak az olduğunu saptadık.

Anahtar Kelimeler: Ovaryan hiperstimülasyon sendromu; ovulasyon indüksiyonu; gebelik; infertilite; laparoskopi

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Yazışma Adresi/*Correspondence:*
Cihan ÇETİN
Bahçeşehir University Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, TURKEY
cihancetin00@yahoo.com

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women of reproductive age. The incidence is 4-21%.[1] PCOS is the most frequent cause of anovulatory infertility; approximately 75% of such infertility is attributable to the condition, which is a heterogeneous disorder exhibiting wide spectra of clinical symptoms and laboratory findings. Although several efforts have been made by different organizations to establish diagnostic criteria, the Rotterdam consensus criteria are the most widely adopted.[2] These criteria require two of the following three findings: 1) signs of clinical or biochemical hyperandrogenism; 2) chronic ovulatory dysfunction (oligo/anovulation); and 3) polycystic ovarian morphology evident on ultrasonography after exclusion of secondary causes (congenital adrenal hyperplasia, nonclassical adrenal hyperplasia, idiopathic hyperandrogenism, idiopathic hirsutism, hyperprolactinemia, thyroid diseases, androgen-secreting tumors, and Cushing's disease).[3] When treating infertile PCOS patients, the initial management option includes lifestyle interventions to achieve weight loss, along with regular physical exercise. If these are unsuccessful, induction of ovulation with clomiphene citrate is considered as first-line therapy. Induction of ovulation with gonadotropins or laparoscopic ovarian surgery (drilling) is second-line therapies for patients resistant to clomiphene citrate.[4,5] Laparoscopic ovarian drilling (LOD) is a less invasive modification of ovarian wedge resection; the ovarian stroma is destroyed during the procedure. The aim is to enhance follicular development and ovulation by reducing androgen and luteinizing hormone (LH) levels and increasing those of follicle-stimulating hormone (FSH) and sex hormone-binding globulin.[6] LOD allows long-term correction of the metabolic and androgenic profile with a low risk of development of ovarian hyperstimulation syndrome (OHSS). Although several studies comparing laparoscopic ovarian drilling and induction of ovulation with gonadotropin as second-line treatments have appeared, meta-analyses have revealed that further studies comparing the efficacies and complications of the two treatments are required.[6,7]

Herein, we describe our clinical experience and compare the effectiveness and outcomes of LOD and induction of ovulation with gonadotropins in PCOS patients resistant to clomiphene citrate.

MATERIAL AND METHODS

The records of patients admitted to the Infertility Outpatient Clinic, University of Cukurova School of Medicine, Department of Assisted Reproductive Treatment Center, between January 2002 and July 2015, with PCOS resistant to clomiphene citrate, were retrospectively reviewed. Patients who met the following criteria were enrolled:

1) Age 20-35 years.

2) A history of infertility at least 1 year in duration.

3) A diagnosis of PCOS using the Rotterdam criteria.

4) Failure to ovulate during at least three cycles of clomiphene citrate treatment.

5) Induction of ovulation by gonadotropins. Recombinant FSH was given using a low-dose step-up protocol. A low dose of FSH (37.5-75 IU/day) was given on the third day of the menstrual cycle, and the dose was increased by 50-100% of the previous dose every 7 days. Recombinant human chorionic gonadotropin was given when one or two follicles with a mean diameter of 18 mm were apparent on transvaginal ultrasonography. Coitus was recommended after 36 h following human chorionic gonadotropin administration.

6) Patients who underwent LOD under general anesthesia. Each ovary was punctured vertically five times using a monopolar cautery device fitted with a 3-mm-diameter probe, and 30 W of energy was applied for 4 s to each hole. A single experienced surgeon (M.T.C.) performed all procedures.

The exclusion criteria were:

1) Any concomitant chronic endocrine disease (diabetes, hyperprolactinemia, hypothyroidism, hyperthyroidism, hypogonadotropic hypogonadism, adrenal disease);

2) Any Müllerian anomaly;

3) Uterine, tubal, or ovarian pathology (myoma uteri, endometriosis, adenomyosis, hydrosalpinx, pelvic tuberculosis, or an ovarian tumor);

4) A history of male infertility;

5) A history of intrauterine insemination (IUI) and in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI);

6) Body mass index (BMI) >35 kg/m^2.

Medical (induction of ovulation with exogenous gonadotropins) and surgical (LOD) options were offered as second-line therapies to all PCOS patients resistant to clomiphene citrate. The expected benefits and possible drawbacks of each therapy were thoroughly discussed with the couples, and the final treatment was primarily influenced by each patient's clinical characteristics and preferences. All women treated with LOD were followed up on regular sexual intercourse for 1 year without receiving any ovulation induction agent. A total of 124 women met the study criteria; of these, 33 constituted the LOD group, and 91 the gonadotropin group. Patient age, the duration of infertility, fasting glucose and insulin levels, hormone and androgen profile, ovarian volume, antral follicle count, level of hemoglobin A1c (Hba1c), BMI, hirsutism score (the Ferriman-Gallwey score), and the numbers of clinical pregnancies and live births were obtained from medical records. All patients were evaluated for antral follicle count and ovarian volume calculation using transvaginal ultrasonography on days 2-5 of the cycle with the ALOKA ultrasound machine with a 7 MHz vaginal probe. The ovarian volume calculation was performed by one experienced gynecologist (I.F.U) as follows: length × width × height × 0.523.[8] Only moderate and severe OHSS cases were recorded in the clinical database, and OHSS classification was performed according to staging system of Golan et al.[9] And all laboratory measurements were performed in the same reference laboratory.

Ethical consideration: The study was approved by the ethics committee of Cukurova University Faculty of Medicine (2015/A-69).

Statistical analysis: The statistical software Statistical Package for the Social Sciences, version 22.0, SPSS Inc, New York, USA (SPSS) was used for all data analysis. Qualitative data are shown as means with standard deviations, and quantitative data as numbers with percentiles. Normality of the data distribution was checked using the Shapiro-Wilk test. The t-test was employed to evaluate the significance of differences between the study and control groups. The Mann-Whitney U-test was used to compare data when the dependent variables were not normally distributed. Correlation analyses were performed using Spearman's test. A p-value <0.05 was considered to reflect statistical significance.

RESULTS

During the study period, 1552 PCOS patients were admitted to the Infertility Outpatient Clinic, University of Cukurova School of Medicine, Department of Assisted Reproductive Treatment Center; 124 met the study criteria. The demographic, clinical, and endocrinological features of 33 patients treated via LOD and 91 patients treated with gonadotropins are summarized in Table 1. There was no significant difference in patient age, BMI, duration of infertility, basal FSH level, LH/FSH ratio, or antral follicle count between the groups. The basal LH and testosterone levels and the mean total ovarian volume were significantly higher in the LOD group. The endocrinological parameters of the two groups, including the fasting glucose and insulin levels, the Hba1c level, and the hirsutism scores, were similar.

The basal FSH level, LH/FSH ratio, and ovarian volume were similar in the two groups in the second and sixth month of treatment, whereas the 6-month basal LH and total testosterone levels were significantly lower in the LOD group. Significant reductions in ovarian volume and LH and total testosterone levels were evident between the second and sixth months of treatment in the LOD group ($p=0.011$, $p<0.001$, and $p=0.002$ respectively). Eight patients (8.7%) developed OHSS in the gonadotropin group, but no LOD patient developed OHSS. The clinical pregnancy, abortion, and live

TABLE 1: Demographical, clinical, and endocrinological parameters of the LOD and gonadotropin groups.

	LOD (n=33)	Gonadotrophin (n=91)	p-value
Age (years)*	28.3±4.6	28.1±4.5	0.206
BMI (kg/m²)*	29.0±4.6	28.9±5.3	0.469
Infertility duration (years)**	5 (1-14)	5 (1-17)	0.317
Basal FSH (D3)(IU/L)*	6.3±1.5	5.7±1.1	0.197
Basal LH (D3) (IU/L)*	12.1±4.9	10.0±5.5	0.012
Basal LH/FSH (D3)*	2.0±1.7	1.7±1.5	0.225
Total testosterone (ng/mL)*	0.8±0.6	0.5±0.3	0.019
Antral follicle count*	14.9±1.3	15.9±2.1	0.472
Mean total ovarian volume (mL3) *	21.0±6.7	13.2±3.1	0.030
Fasting glucose (mg/dL)*	94.7±14.9	93.0±17.0	0.413
Fasting insulin (mU/L)**	14.0 (4.5-34.0)	17.4 (9.0- 36.7)	0.186
Hba1c (%)**	5.4 (5.0-6.1)	5.4 (5.0-8.7)	0.333
Hirsutism score**	10 (8-12)	11 (8-14)	0.449

*Mean±standard deviation; **median (minimum-maximum).

LOD: Laparoscopic ovarian drilling; BMI: Body mass index; FSH: Follicle-stimulating hormone, LH: Luteinizing hormone; HbA1c: Hemoglobin A1c; D3: Day 3 of the menstrual cycle.

birth rates were similar between the two groups. Of the 91 patients allocated to the gonadotropin treatment, 71.5% (206 of 288) of the cycles were ovulatory. Reasons for cancellation of the 82 cycles were he poor response (36 cycles), he risk of ovarian hyperstimulation syndrome (23), the risk of multiple pregnancies (16), and other (7). For each patient, the mean duration of stimulation was 15.4 (3.9 SD) days and for the use of recombinant follicle stimulating hormone was 1837 (695 SD) IU. Of the 35 ongoing pregnancies in the gonadotropin group, nine (%25.7) were multiple pregnancies. Laboratory data on each group in the second and sixth months of treatment, the OHSS rates, and the clinical and live birth rates are summarized in Table 2.

DISCUSSION

The most important feature of LOD is a reduction in the conversion of androgens to estrogen in peripheral tissues. The androgen-producing ovarian tissue is efficiently destroyed by means of ovarian wedge resection. An androgen-dominant follicular environment is thus rendered estrogen dominant, and the hormonal environment is restored by correcting the ovarian-pituitary feedback mechanism.[10-12] These local and systemic effects improve follicular development and ovulation. We compared LOD with exogenous gonadotropin treatment; both are second-line treatment options for infertile PCOS patients resistant to clomiphene citrate. We found that ovarian volume and both LH and total testosterone levels improved significantly in LOD patients compared to the pretreatment values. Similarly, Amer and co-workers reported significant reductions in the serum LH level, the LH/FSH ratio, and testosterone, androstenedione, and free androgen indices, and an unchanged serum FSH level after LOD in PCOS patients. They also recorded significant mid-term (1-3 yr) and long-term (4-9 yr) improvements in reproductive outcomes in one-third of patients treated via LOD.[8]

We found that LOD and exogenous gonadotropin treatment were associated with similar abortion and live birth rates, but LOD was associated with less OHSS and multiple pregnancy rates. Similarly, Eftekhar et al. retrospectively investigated the effects of LOD in 300 patients with clomiphene-resistant PCOS and found a significant reduction in the OHHS risk in those patients compared with patients who underwent medical treatment, although the pregnancy rates were similar in the two groups.[5] Also, a recent systematic review revealed that multiple pregnancy rates differ from

TABLE 2: Post-treatment laboratory data, complications, and pregnancy outcomes of the LOD and gonadotropin groups.

	LOD (n = 33)	Gonadotrophin (n = 91)	p-value
2-month basal FSH (D3) (IU/L)*	6.4±1.0	6.1±1.3	0.697
6-month basal FSH (D3) (IU/L)*	6.1±2.9	5.6±2.5	0.142
2-month basal LH (D3) (IU/L)*	9.1±4.3	9.1±5.2	0.753
6-month basal LH (D3) (IU/L)*	7.2±3.1	9.0±7.6	<0.001
2-month basal LH/FSH (D3)*	2.0±1.7	1.7±1.5	0.225
6-month basal LH/FSH (D3)*	1.5±0.6	1.5±1.0	0.345
2-month total testosterone (ng/mL)*	0.5±0.2	0.4±0.2	0.317
6-month total testosterone (ng/mL)*	0.4±0.1	1.2±1.3	<0.001
2-month ovarian volume (mL)*	15.2±7.4	12.6±3.0	0.395
6-month ovarian volume (mL)*	14.7±7.4	12.7±3.4	0.176
OHSS**	0 (0)	8 (8.7)	<0.001
Clinical pregnancies**	10 (30.3)	42 (46.1)	0.056
Abortions**	2 (6.1)	7 (7.7)	0.114
Live births**	8 (24.2)	35 (38.5)	0.069
Multiple pregnancies**	0 (0)	9 (25.7)	<0.001

*Mean ± standard deviation; **n (%)

LOD: Laparoscopic ovarian drilling; FSH: Follicle-stimulating hormone, LH: Luteinizing hormone; D3: Day 3 of menstrual cycle; OHSS: Ovarian hyperstimulation syndrome.

0% to 10% after LOD procedure and it is significantly lower than gonadotropin therapy that makes LOD procedure more attractive option in PCOS patients resistant to clomiphene citrate.[13] But, the other pregnancy complications including gestational diabetes mellitus and pregnancy-induced hypertension have been reported similar between LOD and other medical treatment options.[14,15] Gonadotropins or other medical agents can cause multiple pregnancies and OHSS in clomiphene citrate-resistant PCOS patients when excessive numbers of follicles are produced during induction of ovulation. In a Cochrane review, Farquhar and colleagues showed that LOD was efficacious and safe in PCOS patients resistant to clomiphene citrate and that it was associated with a significant reduction in the number of multiple pregnancies (OR 0.13; 95% CI 0.03-0.52; five trials, n=166) and risk of OHSS (OR 0.14; 95% CI 0.02-1.19; seven trials, n=908) compared to gonadotropin treatment; the abortion and pregnancy rates were similar in the two groups. It was concluded that clinical decisions on LOD should be made after consideration of local circumstances, adverse effects, costs, and patient preferences.[16]

Exogenous gonadotropins used to treat PCOS patients resistant to clomiphene citrate afford high rates of pregnancy and live birth, but are associated with high maternal and fetal mortality rates, a high frequency of OHSS, a risk of multiple pregnancies, difficulties with patient compliance due to the high costs and the need for close monitoring.[17-19] We found that the LOD and exogenous gonadotropin groups had similar cumulative pregnancy rates. Similarly, De Frene et al. compared the pregnancy rates of 43 women in whom ovulation was induced with human menopausal gonadotropin and 35 who were treated via LOD; the ongoing pregnancy rates were similar (60% and 69.8%, respectively).[20] Also, Bayram and colleagues reported a pregnancy rate of 49% of women treated with clomiphene citrate/electrocautery and 67% in those given recombinant FSH, in a randomized controlled trial.[21] In a study of PCOS patients resistant to clomiphene citrate, Goudarzi and co-workers reported similar pregnancy rates in LOD groups and groups in whom ovulation was induced with gonadotropins (OR: 0.534; 95% CI: 0.242-1.176; p=0.119; six studies, n=499, I^2=73.201%). They speculated that the significant reductions in live birth rates in the LOD

groups were attributable to high rates of multiple pregnancies in the gonadotropin groups (OR: 0.446; 95% CI: 0.269-0.74; p=0.02; three studies, n=318, I^2=3.353%).[6]

Although LOD increases ovulation and sensitivity to ovulation-stimulating agents, some concerns remain. The long-term effects on the ovaries are unclear, general anesthesia is required, post-surgical adhesion risks are present, and there may be a negative effect on the ovarian reserve.[22-24] We performed bilateral LOD with a small number of perforations (five for each ovary), followed by a short period (4 s) of low energy delivery (30 W per hole). To reduce heat damage to surrounding tissues and adhesion formation, we performed abdominal lavage using Ringer's lactate solution; 200 mL of the solution was left in Douglas pouch after the operation. Gomel et al. reported that the use of abdominal lavage and insulated electrocautery needles during ovarian drilling reduced adhesions; they emphasized the importance of performing the procedure carefully, respectfully, appropriately, and traumatically.[25]

In conclusion, we found that the pregnancy rates were similar between PCOS patients resistant to clomiphene citrate treated via LOD and those in whom ovulation was induced with exogenous gonadotropins (second-line therapies). The risk of OHSS and multiple pregnancies was significantly lower in the former group of patients. Thus, LOD is a safe and effective alternative to gonadotropin therapy without the risk of OHSS and multiple pregnancies. Also, we thought that performance of the procedure with the experienced reproductive specialists by following the minimally invasive surgical steps of the operation strictly would be beneficial for achieving better clinical outcomes with fewer side effects. Furthermore, comprehensive counseling of these patients about the advantages and disadvantages of the two treatment options is crucial. The experience of our center would be useful as a tool for counseling of PCOS patients resistant to clomiphene citrate when considering the second-line treatment options.

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Conflict of interest

The authors declare that there is no conflict of interest.

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