Laparoscopic Ovarian Drilling in Metformin and Clomiphene Resistant Women with Polycystic Ovarian Syndrome

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Abstract

Objective: The study aimed to evaluate the effectiveness of laparoscopic ovarian drilling (LOD) on ovulation and restoration of menstrual cycles and pregnancy.

Materials and methods: This cross sectional study was conducted on 81 consecutive Polycystic Ovarian Syndrome (PCO) patients whom were referred to Avesina Infertility clinic during 2003-2006. Exclusion criteria were tubal and male factor infertility, hyperprolactinemia, thyroid disease and diabetes mellitus. Patients with the age range of 20-35, body mass index of less than 35 kg/m^2, failure to ovulate during at least three cycles of Clomiphene Citrate (CC) consumption and more than 12 months of ovulatory factor infertility entered the study. Metformin was used for at least 8 weeks in combination with CC. Forty four PCO women who had not ovulated after medical therapy with combination of CC and Metformin were selected for LOD. The data was analyzed with SPSS software using t- test and logistic regression analysis. P<0.05 was considered statistically significant.

Results: Patients aged 28.9±2.3 years with infertility duration of 4.8±2.3years and BMI of 28±3.3 kg/m^2. Effectiveness of medical therapy significantly was related to BMI (P<0.001). After LOD, ovulation occurred in 14 cases (31.8%), restoration of menstrual cycle in 18 women (40.9%), and spontaneous pregnancy in 5 cases (11.3%).

Conclusion: LOD is a good method for restoration of ovulatory cycles in anovulatory PCOS women who were resistant to the combination of CC and Metformin. LOD may avoid or reduce the need to gonadotropins for ovulation induction.

Key Words: PCOS, Metformin, Clomiphene resistant, Ovarian drilling

Introduction

Polycystic ovary syndrome (PCOS) is the commonest cause of anovulatory infertility affecting 5-10% of reproductive age women (1). Hyperinsulinemia is the commonest contributor to the state of anovulation and its reduction, by weight loss or insulin sensitizing agents such as Metformin chloridrate (an oral biguanid for type 2 diabetes) alone often restores ovulation or improve results in anovulatory clomiphene citrate (CC) resistant patients with PCOS (2). Surgical ovarian wedge resection was the first established treatment

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for anovulatory PCOS patients but was largely abandoned due to the risk of post-surgical adhesions. Laparoscopic ovarian drilling (LOD) introduced by Gjonnaess (1984) restored ovulation in 92% of patients with a pregnancy rate of 69% (3). LOD is performed by using a pointed monopolar or bipolar electrode or laser. LOD can be done on an outpatient basis with less trauma and fewer postoperative adhesions and is proved to be successful for the induction of ovulation, particularly in thin patients with high LH concentrations (4). The mechanism of action of LOD is not fully understood and it seems that ovarian diathermy works by increasing the sensitivity of the ovaries to endogenous FSH and destruction of the androgen producing ovarian stroma plays a key role(4). Also, LOD may avoid or reduce the risk of ovarian hyper stimulation syndrome (OHSS) and multiple pregnancies in comparison to gonadotropins with the same success rate of conception (4, 5). The high pregnancy rate and economic aspect of the procedure offer an attractive management for patients with PCOS. Malkawi et al showed that CC-resistant patients with PCOS can be treated effectively either by Metformin or by LOD (6). Pirwany showed the ovulation and pregnancy rates appear to be similar for both techniques (7). However, unlike LOD, Metformin may decrease the incidence of type 2 diabetes and coronary heart disease (8).

Metformin, an insulin-sensitizing agent, has been used successfully as the first-line drug to induce ovulation in women with PCO and hyperinsulinemia, but Metformin is not always beneficial in clinical practice (7). Previous studies did not show the efficacy of LOD after unsuccessful treatment with combination of metformin and CC in restoration of ovulation or improvement of the results in patients with PCOS. The aim of the present study was to evaluate the efficacy of LOD, after ineffective Metformin administration in the CC resistant women with PCOS, which is the first study in this regard.

Table 1: Results of LOD in PCO patients resistant to the combination of Clomiphene and Metformin

	n (%)
Before LOD	
Metformin + clomiphene responsive	37 (45.6)
Metformin + clomiphene resistant	44 (54.4)
After LOD	
Spontaneous ovulation	14 (31.8)
Restoration of menstrual cycles	18 (40.9)
Spontaneous pregnancy	5 (11.3)
Pregnancy with induction of ovulation	9 (20.4)

Materials and methods

This cross sectional study was performed from August 2003 till November 2006 at Avesina infertility clinic. The investigation has been approved by ethical committee of Avesina research institute and the relevant consent was obtained from the patients. Infertile PCOS women (20-35 years old) with the history of ovulation failure with at least 3 months taking CC were studied. All of the infertile women, who met the clinic, consecutively were considered in our study. They were assessed by history, physical exam, routine lab measurements (plasma FSH, LH and Estradiol or E2 at 3th day of the cycle, Fasting blood sugar or FBS, Fasting insulin, Thyroid function tests, Prolactin) , hysterosalpingography (HSG) and also 5 MHz transvaginal sonography in the early follicular phase. The criteria for PCOS were chronic anovulation (with amenorrhea or oligomenorrhea) and hyperandrogenism (with hirsutism) according to NIH criteria (9). Exclusion criteria were: Male factor and tubal factor infertility (ruled out by spermogram and HSG), hyperprolactinemia, thyroid disease and diabetes. Inclusion criteria were: 1) age of 20-35 years, 2) body mass index less than 35 kg/m^2, 3) Failure to ovulate with CC (150 mg of CC for 5 days in the early follicular phase) during at least three cycles, 4) Ovulatory factor infertility for more than one year.

The patients were treated for 3 months with Metformin 1500mg/d (tab 500 mg, Parsminoo CO) and after at least 8 weeks CC 100-150mg/d was added. Patients, who had not ovulated after medical therapy with combination of Metformin and CC, were prepared for LOD. We informed all cases about the technique, therapeutic effects and potential risks of laparoscopy and ovarian drilling. Each ovary was cauterized at 10-15 points for 3-4 seconds using high frequency monopolar 10 mm microneedle. Results of the treatment in terms of ovulation, restoration of menstrual cycle and clinical pregnancy (spontaneous and /or with induction of ovulation) were observed over the 6 months period.

Data analysis was performed by SPSS software using t-test and logistic regression analysis. Data were presented as mean ± SD for numerical variables and in percentage for categorized variables. $P<0.05$ was considered significant.

Table 2: Characteristics of patients (n=81)

	Pregnancy with ovulation induction	Spontaneous pregnancy	After ovarian drilling			
			Ovulation	Menstrual restoration	Responsive to medication	Resistant to medication
Age (year)	28.9±2.3	29±2.5	28.7± 2.6	28.7±2.6	29.2±3.2	27.5 ±2.1
BMI (kg/m^2)	28±3.3	26.5±2.3 [a]	26.9±2.2	26.9±2.2	25.8±3.2	30.5±2.5 [b]
Duration of infertility (year)	4.8±2.3	4.7±2.4	4.8±2.1	4.8±2.4	3.8±1.4	2.3±1.4 [c]

Values are presented as Mean±SD , [a] P-Value <0.001 , [b] P-Value=0.016 , [c] P-Value=0.001

Results

Eighty one women aged 28.9±2.3 years with infertility duration of 4.8±2.3 years, BMI of 28±3.3 kg/m^2 and LH/FSH >2 entered the study. They suffered from PCO syndrome and hyperinsulinemia (Fasting Insulin/FBS : >25/100). Hirsutism was reported in 66 cases (81.4%).

Forty four PCOS patients (54.4%) were refractory to the combination of Metformin and CC, whom were selected for LOD. Ovulation and restoration of menstrual cycle were measured in first 6 cycles after LOD. The response in terms of ovulation and restoration of menstrual cycles and pregnancy are measured and shown in table 1. Five patients became spontaneously pregnant in the first 2 months after LOD without any medication. Also the results of the treatments in relation to characteristics of the patients are shown in table 2. In our study, a positive correlation was found between responsiveness to Metformin and CC, and BMI, using logistic regression model, OR=1.34 (95% CI: 1.13-1.58). Also mean BMI was significantly lower in patients who responded to Metformin and CC (P<0.001) (table 2). Rate of spontaneous pregnancy was not significantly related to age, duration of infertility or BMI. After LOD, 14 patients showed signs of spontaneous ovulation which was confirmed by sonography (on 12-15th day of menstrual cycle) and again was not related to the above mentioned variables (NS). The rest of the patients (n=25) received CC and/or CC and hMG for induction of ovulation, thereafter all patients ovulated in the observation period. Interestingly, the mean BMI and mean duration of infertility were different in pregnant patients whom underwent LOD and induction of ovulation (p=0.016, p=0.001, respectively) in this study.

Discussion

PCOS is a heterogeneous disorder in which chronic anovulation, hyperinsulinemia, insulin resistance and also obesity are common associated features (10). A growing body of evidence has suggested that serum hyperinsulinemia contributes to the excess ovarian androgen secretion observed in women with PCOS (11). Also, a positive correlation was found between insulin levels and BMI ($p < 0.01$) in Draveka I study. The standard therapy for anovulatory women with PCOS is oral administration of CC (12). Also, Metformin chloridrate often restores ovulation or will improve results in anovulatory CC resistant patients with PCOS (13, 14). However, a significant proportion of women with PCOS fail to ovulate with the combination of standard dosage of CC (CC-resistant PCOS) and Metformin. We reported 45.6% ovulation rate after using Metformin and CC in our study. However, 54.4% did not respond to the medical treatment. Also our study showed a positive correlation between responsiveness to Metformin and CC, and BMI (table 2). Draveka et al showed a statistically significant difference in insulin levels of slim (BMI less than 25) as compared with obese women (BMI more than 30 kg/m^2) ($p < 0.01$). Also he showed that metformin treatment could decrease insulin level with subsequent normal menstrual cycle in 68.7% of patients with hyperinsulinemia (12) which is more than the result of our study (45.6%). This difference might be related to racial differences. We observed the results of LOD after unsuccessful treatment with Metformin and CC which was a unique study in this regard. Although a variety of medical therapies exist for restoration of ovulation (15) the role of LOD as second-line treatment in women with PCOS after failure of medical therapy is unclear. There are some studies comparing the effectiveness of LOD and medical treatment in PCOS patients. Al-Fadhli R and Tulandi T (16, 17) discussed the place of LOD versus medical treatment with Metformin for patients with PCOS. Some data suggest that treatment with Metformin is equally as effective as LOD (7), however, Palomba, showed that

Metformin administration was more effective than LOD in overall reproductive outcomes in overweight infertile CC-resistant women with PCOS (18). The mechanism of action of LOD is unclear; and its beneficial effect is apparently due to destruction of the androgen-producing stroma which results in a decrease in ovarian stromal blood flow and subsequently serum level of Vascular Endothelial Growth Factor (VEGF), Insulin Like Growth Factor-1(IGF-1) and LH which are significantly high in patients with PCOS (17). Also, Ahmed et al showed that LOD reduces the VEGF, IGF-1 and LH with little or no effect on insulin sensitivity and lipoprotein profile and also reduces the blood flow velocities which may explain the reduction of risk of ovarian hyper stimulation syndrome in patients with PCOS (19). It has been shown in Palomba S et al study, the majority (56-94%) of PCOS patients who were CC resistant, ovulate after drilling, and at least half of them go on to achieve pregnancy. Predictive factors for pregnancy were younger age and lower body mass index (18). Interestingly our study showed significant positive relation between BMI and pregnancy rate with induction of ovulation after LOD. However, no significant relation was observed between age and ovulation and pregnancy after LOD. Gomel V, Yarali H showed LOD is associated with an ovulation rate of approximately 80% and a pregnancy rate of 50-60% within first year of the procedure (20). However, a percentage of patients as high as 43% may not ovulate spontaneously after LOD (18). The present study showed 31.8% ovulation rate and 11.3% spontaneous pregnancy rate after LOD, which is lower than the rate of above mentioned studies. This findings might be related to the shorter period time (6 months) of follow up.

We experienced LOD as a good method in patients who did not respond to metformin and CC. LOD may avoid or reduce the need to gonadotropins for ovulation induction. However, the use of LOD apart from the usual risks of laparoscopy and general anesthesia may induce peri-adnexal adhesions in 19-43% of patients (21, 22), and theoretically to premature ovarian failure.

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