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ORIGINAL ARTICLE

Unilateral Versus Bilateral Laparoscopic Ovarian Drilling Using Thermal Dose Adjusted According to Ovarian Volume in CC-Resistant PCOS, A Randomized Study

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Abstract

Objective This study aimed to evaluate the efficacy of unilateral laparoscopic ovarian drilling versus bilateral laparoscopic ovarian drilling with thermal dose adjusted according to ovarian volume in clomiphene citrate (CC)-resistant PCOS patients in terms of endocrine changes, menstrual cycle resumption, ovulation and pregnancy rates.

Patients and Methods This study was conducted in the Department of Obstetrics and Gynecology, Zagazig university hospitals. One hundred CC-resistant PCOS patients were divided into two groups. Group (I) (50 patients) underwent unilateral laparoscopic ovarian drilling with thermal dose adjusted according to ovarian volume (60 J/cm^3 of ovarian tissue), and group (II) (50 patients) underwent bilateral laparoscopic ovarian drilling using the same previously mentioned thermal dose. Endocrinal changes and menstrual cycle resumption were assessed within 8 weeks postoperatively, but the ovulation and pregnancy rates were estimated after 6-month follow-up period.

Results There was no statistically significant difference between the two groups as regards demographic data ($p > 0.05$). As regards menstruation cycle resumption (62.5 vs. 81%) ($p = 0.047$), total ovulation rate (54.2 vs. 78.7%) ($p = 0.011$) and cumulative pregnancy rate (33.3

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vs. 55.3%) ($p = 0.031$), there was statistically significant difference between both groups. After drilling, there were highly statistically significant decrease in the mean serum levels of luteinizing hormone (LH) and significant decrease in the mean serum levels of testosterone in both groups. Mean serum level of follicle stimulating hormone (FSH) did not change significantly in both groups after drilling.
Conclusion Bilateral laparoscopic ovarian drilling with thermal dose adjusted according to ovarian volume is more effective than the right-sided unilateral technique with thermal dose adjusted according to ovarian volume in terms of menstrual cycle resumption, ovulation and cumulative pregnancy rates in CC-resistant PCOS patients.

Keywords Laparoscopic ovarian drilling · Thermal dose adjusted · Polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is responsible for more than eighty percent of anovulatory infertility and 5–10% of infertile women at all [1]. The primary outcome measure of PCOS-related infertility treatment is the ovulation, pregnancy, and delivery of a healthy child [2]. Lifestyle modifications and physical exercises are essential to weight loss in the obese PCOS patients. Clomiphene citrate is considered the first line of infertility treatment, the second line includes gonadotropins or laparoscopic ovarian drilling (LOD), and the third is assisted reproductive techniques [3].

Ovulation failure after administration of 150 mg CC daily for 5 days starting on the third day of the cycle is defined as CC resistance [4].

Laparoscopic ovarian drilling (LOD) is preferable than gonadotropins as it results in monovulation, so there is no risk of multiple pregnancy or ovarian hyperstimulation syndrome (OHSS) [5]; furthermore, spontaneous ovulation occurs in some patients without any additional interference [6] and no negative effect on ovarian reserve, as shown by the markers of ovarian reserve such as FSH and AMH during the follow-up period [7]. Adnexal adhesions and reduced ovarian reserve are considered two probable hazards of LOD [8–11].

Unilateral ovarian drilling is equally efficacious as bilateral ovarian drilling in inducing ovulation and achieving pregnancy. Unilateral ovarian drilling may be a suitable option in clomiphene citrate-resistant infertility patient of PCOS which can replace bilateral ovarian drilling with the potential advantage of decreasing the chances of adhesion formation [10, 12, 13].

The clinical response to LOD seems to be thermal energy dose-dependent. Two punctures (300 J) per ovary are associated with poor results. Between three and five (450–750 J) punctures per ovary seem to represent the effective thermal dose. The application of six or more (≥900 J) punctures per ovary may result in excessive destruction to the ovary and should therefore be discouraged [14].

Laparoscopic ovarian drilling with four punctures delivers 640 Joules/per ovary widely accepted by many investigators. However, the optimum amount of electrosurgical energy needed during LOD to achieve maximum reproductive outcome without risks is uncertain [5].

The pregnancy rate following LOD is more than 50% in CC-resistant PCOS; hence, it can be concluded that LOD reduces the need for ART by 50% in CC-resistant PCOS and is a safe option, especially for women who cannot afford the cost of ART [15]. Dose-adjusted ULOD applied to the larger ovary has comparable ovulation and pregnancy rates to fixed dose BLOD at 3-month follow-up periods with decrease in its effectiveness after 6 months [16].

Development of postoperative adhesion is a widespread consequence of surgical trauma and healing following open or laparoscopic gynecological surgery and is associated with significant complications. To avoid formation and reformation of adhesions using anti-adhesive agents as auto cross-linked hyaluronic acid gel barrier appeared to be a reasonable, effective and easily applied with high safety profile substance that can help in reducing formation of adhesions after laparoscopic ovarian drilling for PCOS patients [17].

The adjusted diathermy dose based on ovarian volume for laparoscopic ovarian drilling of polycystic ovary syndrome has a better ovulation and pregnancy rates compared with fixed energy dose [18].

Patients and Methods

This randomized clinical study was conducted in the cytogenetic and endoscopy unit at the Department of Obstetrics and Gynecology, Zagazig university hospital, in the period extended from November 2015 and January 2017, last 6-month follow-up. This study was approved by the Ethical Committee of Zagazig university hospitals, Egypt. All participants provided an informed written consent before recruitment in the study.

The sample size was estimated depending on the expected ovulation rate as a primary outcome. Zakherah et al. [18] used a thermal dose of (60 J/cm^3 of the ovarian tissue) to achieve ovulation 81.8%. On the assumption that a 20% ovulation difference with adjusted thermal dose based on ovarian volume will be clinically relevant, we needed a total 100 patients to demonstrate this difference

with a statistical significance of a alpha = 0.05 and beta = 0.2. The participants were divided randomly into two groups. The first group (50 patients) underwent unilateral laparoscopic ovarian drilling on the right side using thermal dose adjusted according to ovarian volume (group I), while the second group (50 patients) underwent bilateral laparoscopic ovarian drilling using thermal dose adjusted according to ovarian volume on both sides (group II).

All participants showed the following selection criteria: infertile women who have CC-resistant polycystic ovary syndrome (150 mg/daily for 5 days), their age within 25–35 years during the study period, infertility duration of ≤3 years. Additionally, body mass index <30 kg/m^2, luteinizing hormone ≥10 IU/ml or LH/FSH ratio ≥2, free androgen index ≥4, normal semen analysis in the husband and normal oral glucose tolerance test. Exclusion criteria were hyper-androgenic disorders like late onset congenital adrenal hyperplasia, hyperprolactinemia, thyroid diseases, and Cushing's syndrome and androgen-secreting tumors. PCOS was diagnosed according to the following criteria [3]: oligomenorrhea and/or amenorrhea; clinical and/or biochemical signs of hyperandrogenism; and transvaginal sonographic appearance of polycystic ovaries (12 follicles or more and 2–9 mm in their diameter or an ovarian volume ≥10 cm^3).

The size of each ovary was estimated according this formula: length × width × height × 0.523 [21]. In this study, we used Voluson 730 pro V ultrasound machine (GE healthcare, Austria with a 3.5 MHz sector transducer for TAS and 7.5 MHz sector transducer for TVS).

Laparoscopic drilling was performed under general anesthesia as follows: 10-mm subumbilical entry and two 5-mm secondary ports in the lower part of the abdomen just above the anterior superior iliac spine. The laparoscope was introduced through the subumbilical port, and secondary ports were used for introduction of the instruments. For the procedure, we used an Evis Exera II video system center model CV-180 with a UES-40 electrosurgical unit and a Monopolar HF electrode needle (Karl Storz, Tuttlingen, Germany).

The right ovary was treated in the group (I), because LOD on the left side was associated with increased risk of adhesions formation (at a rate of 64%;) and the oocytes originating from the right ovary have a greater fertility potential [22].

The thermal dose received by the ovary for ULOD or BLOD was calculated with use of the following suggested model. In this study, similar needle penetration depth was used; the least effective thermal dose was 600 J per ovary [18]. The reported ovarian volume mean was 10.8 cm3 (range of mean 9.6–12.0 cm3) [7]. We are planning to use the least thermal effective dose which is 625 J/10.8 cm3 = 60 J/cm3 of ovarian tissue.

The number of punctures (*N*p) per ovary was calculated according to the following formula: N_p = 60 J/cm3/30 W × 4 s.

Immediately after drilling, ovaries were irrigated by 500 ml isotonic saline solution for prevention of adhesions. So, patients in both groups received different numbers of punctures with variable thermal doses.

Hormonal assay (LH, FSH and testosterone levels) was performed in the early follicular phase (3rd day menstrual cycle) of the 1st postoperative spontaneous menstruation (which occurs within 8 weeks after the operation). In non-menstruating patients, hormonal assay was performed after induction of menstruation using 100-mg I.M. progesterone injection (3rd day of induced cycle). In menstruating patients, if ovulation did not occur within 10 weeks postoperatively, ovulation induction was done using incremental doses of clomiphene citrate up to 150 mg/day for 5 days starting from 3rd day of the cycle. In non-menstruating patients, ovulation induction was started in 3rd day of the induced menstruation using the previously mentioned regimen. Ovulation was assessed by serial TVS until visualization of pre-ovulatory follicle (at least 18 mm). Ovulation was confirmed by seeing follicular collapse on subsequent TVS follow-up, appearance of fluid in cul-de-sac and elevated mid-luteal serum progesterone level (>5 ng/ml).The cumulative pregnancy rate was assessed after 6-month follow-up period. Pregnancy was identified by positive serum pregnancy testing plus appearance of intrauterine gestational sac.

Statistical Analysis

Data were checked, entered and analyzed using SPSS version 20 for data processing. Qualitative data were analyzed using the frequency and percentage. Quantitative data were assessed by mean ± standard deviation (SD). We used Chi-square test and *t* test for comparison between the studied groups. *P* value <0.05 is considered significant, and *P* value >0.05 is considered non-significant.

Results

One hundred PCOS women were classified into two groups (I, II). Group I (50 patients) performed ULOD with 2 patients excluded; one patient had a tubal disease which was identified during laparoscopy and the other patient missed the follow-up. Group II (50 patients) performed BLOD. One patient was excluded due to endometriosis which was diagnosed during laparoscopy, and another two patients missed

follow-up. Forty-eight patients in group I and 47 in group II were included in the final analysis (Fig. 1).

The demographic characteristics of the studied groups are shown in (Table 1). No significant difference was found between the studied groups as regards age, duration of infertility, mean ovarian volume and hormonal assays. After LOD, 30 (62.5%) patients in group I and 38 (81%) patients in group II experienced spontaneous resumption of menstruation within 8 weeks with statistically significant difference between both groups ($p = 0.047$) as shown in (Table 2).

As regards ovulation in the spontaneous menstrual cycle (spontaneous or induced ovulation), 18 (60%) patients in group (I) and 32 (84.2%) patients in group (II) showed ovulation with statistically significant difference between both groups ($p = 0.025$). Induction of ovulation using CC in non-menstruating patients (after induction of menstruation) associated with ovulation in 8 (44.4%) patients in group (I) and 5 (55.6%) patients in group (II) with no statistically significant difference between both groups ($p = 0.59$). As regards total ovulation rate, there was statistically significant difference between both groups (54.2 vs. 78.7%) ($p = 0.011$). As regards cumulative pregnancy rate 16/48(33.3%) got pregnant in group (I) and 26/47(55.3%) patients got pregnant in group (II) with statistically significant difference between the both groups ($p = 0.031$).

After drilling, there was highly statistically significant decrease in the mean serum levels of luteinizing hormone (LH) and significant decrease in the mean serum levels of testosterone in both groups. Mean serum level of follicle stimulating hormone (FSH) did not change significantly in both groups after drilling as shown in Table 3.

Discussion

Androgen excess in PCOS is believed to be the result hyperinsulinemia which associated with increased androgen production by ovarian theca cells [19]. The significant decline in postdrilling serum androgens and LH level that is seen in patients who received an adjusted thermal dose could be explained by adequate thermal destruction of androgen-secreting stromal cells. The reduction in LH level leads to decreased ovarian androgen production, which along with increasing FSH level allows appropriate follicular development and ovulation [20] It may be assumed therefore that the ameliorating effect of LOD on androgen and LH levels is influenced by the amount of energy

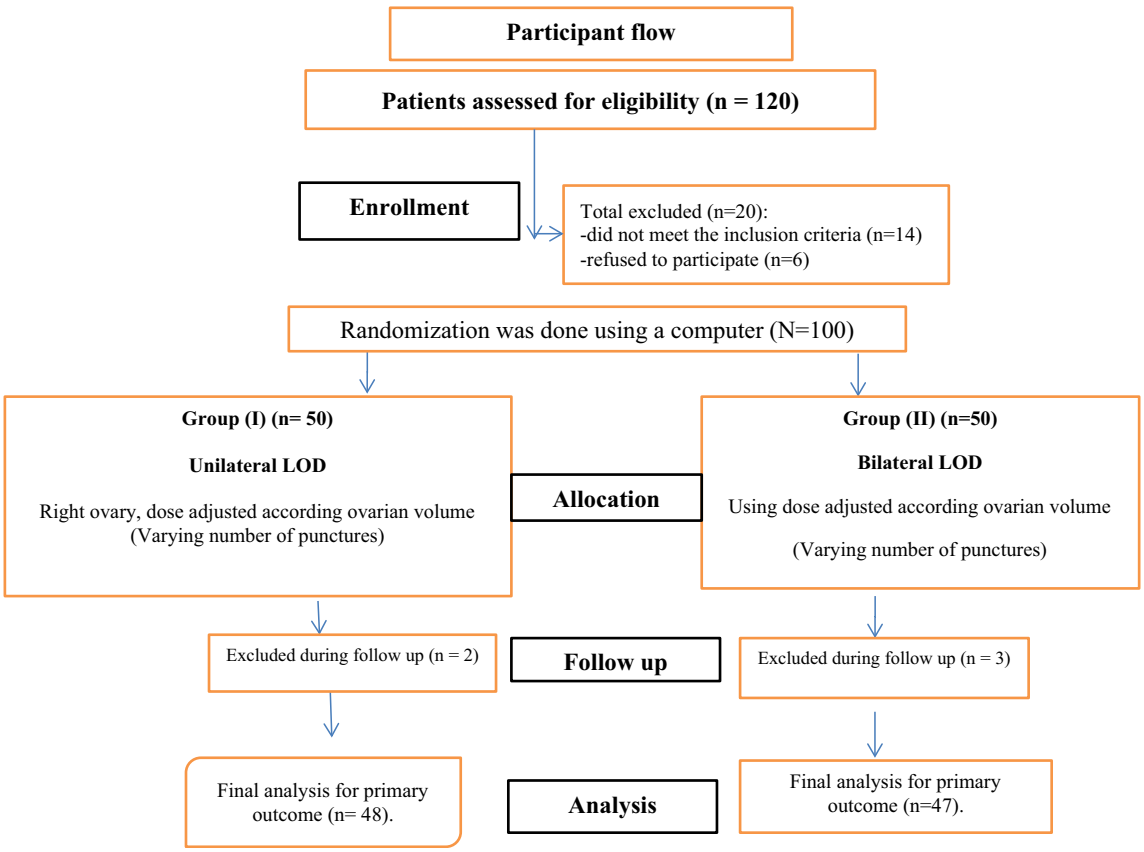

Fig. 1 Flow chart of participant in the study

Table 1 Demographic characteristics of study population prior to thermal dose-adjusted LOD (100)

Parameters	Group (I) (NO = 48)	Group (II) (NO = 47)	*p* value
Age (yrs)	27.5 ± 4.25	28.03 ± 4.32	0.548
Duration of infertility(yrs)	3.04 ± 2.78	4.11 ± 2.56	0.054
BMI (kg/m^2)			
>30	20 (40%)	23 (46%)	0.62
<30	30 (60%)	27 (54%)	
Menstrual cycle			
Amenorrhea	16 (32%)	15 (30%)	0.69
Oligomenorrhea	34 (68%)	35 (70%)	
Ovarian volume			
Mean total ovarian volume(cm^3)	11.5 ± 1.63	11.4 ± 2.74	0.83
Volume of the left ovary(cm^3)	11.3 ± 1.79	11.4 ± 2.63	0.83
Volume of the right ovary(cm^3)	11.6 ± 2.37	11.4 ± 2.34	0.68
Hormonal profile			
LH (IU/L)	11.3 ± 0.5	11.3 ± 0.4	0.29
FSH(IU/L)	5.6 ± 1.5	5.7 ± 2.4	0.81
Total testosterone (nmol/ml)	1.08 ± 0.27	0.96 ± 0.23	0.08

Values are given as mean ± SD. Student's t test was used. BMI = body mass index

Table 2 Menstrual cycle resumption, ovulation and pregnancy rates in the studied population

Variable	Group (I) (NO = 48)	Group(II) (NO = 47)	*p* value
Menstrual cycle resumption[a]			
Spontaneous(68)	30 (62.5%)	38 (81%)	0.047
Induced(27)	18 (37.5%)	9 (19%)	
Total ovulation rate[b]	26/48 (54.2%)	37/47 (78.7%)	0.011
Ovulation rate in spontaneous menstrual cycle (either spontaneous or induced ovulation):[c]	NO = 30(%)	NO = 38 (%)	
Yes	18 (60%)	32 (84.2%)	0.025
No	12 (40%)	6 (15.8%)	
Ovulation rate in induced menstruating cycle(induced ovulation):[d]	NO = 18 (%)	NO = 9 (%)	
Yes	8 (44.4%)	5 (55.6%)	0.59
No	10 (55.6%)	4 (44.4%)	
Cumulative pregnancy rate[e]	16/48 (33.3%)	26/47 (55.3%)	0.031

[a] Two patients in group (I) and three in group (II) excluded during the study

[b] Total ovulation rate in spontaneous or induced menstrual cycle, calculated as the number of ovulatory patients divided by the number participating patients in each group

[c] Ovulation rate in spontaneous menstruating cycle (either spontaneous or induced ovulation): calculated as the number of ovulatory patients divided by the number of spontaneously menstruating patients

[d] Ovulation rate in induced menstruating cycle (induced ovulation): calculated as the number of ovulatory patients divided by the number of patients received induction of menstruation

[e] Cumulative pregnancy rate, calculated as the number of pregnancies divided by the total number of patients (16/48 in group I and 26/47 in group II)

applied to the ovary, and low doses may be associated with lower success rates [21].

Some studies compared ULOD and BLOD with fixed thermal energy and concluded that unilateral LOD has the same response as bilateral LOD as regards ovulation and pregnancy rates. Also, it has the same risk of adnexal adhesions and decreased ovarian reserve [22, 23].

To our knowledge, our study is the first one which compares the efficacy of unilateral LOD on the right side versus bilateral LOD with adjusted thermal dose according to the volume of the ovary in CC-resistant PCOS patients.

Table 3 Hormonal profile before and after LOD in the studied population

p value#	Before LOD	After LOD	Variables
LH (IU/L)			
Unilateral	11.1 ± 0.5	7 ± 2.5	<0.001**
Bilateral	11.4 ± 1.3	6 ± 2.4	<0.001**
p value$	0.14	0.049*	–
FSH (IU/L)			
Unilateral	5.2 ± 1.01	5.3 ± 1.02	0.63
Bilateral	5.3 ± 2.5	5.4 ± 2.60	0.85
p value$	0.8	0.79	–
Testosterone (nmol/L)			
Unilateral	1.8 ± 0.8	1.43 ± 0.75	0.021*
Bilateral	1.9 ± 1.3	0.89 ± 1.7	0.002*
p value$	0.65	0.047*	–

$: *t* test. #: paired *t* test

* Statistically significant (p value < 0.05)

** Statistically highly significant (p value < 0.001)

Adashi et al. [24] showed that BLOD with fixed thermal energy is a standard method of LOD. However, bilateral ovarian activity could be achieved by ULOD and this is due to the effect of different growth factors, especially insulin like growth factor-1, which interacts with FSH and reduces the serum level of LH.

The incidence of adnexal adhesions with LOD differs from 19 to 43%. The risk becomes higher with more thermal damage to the ovarian surface [25]. Reduced ovarian reserve is the second complication of this procedure and depends on drills number (>4–6). So, adnexal adhesions risk besides the rate of reduced ovarian reserve could be reduced by decreasing drills number [10].

In our research, we have studied the effect of unilateral LOD versus bilateral LOD using thermal dose adjusted according to ovarian volume on the menstrual cycle resumption, hormonal state, ovulation and conception rates of 95 CC-resistant PCOS patients during 6-month postoperative follow-up.

In our study, no significant difference was found between the two groups; ULOD and BLOD as regards age, duration of infertility, BMI, preoperative menstrual cycle pattern, ovarian volume and hormonal profile. Patients performed BLOD showed more menstrual cycle resumption, total ovulation and cumulative pregnancy rates when compared to patients performed ULOD (the difference is statistically significantly different). Also, the mean levels of LH showed highly statistically significant decrease and testosterone showed significant decrease after thermal dose-adjusted LOD, but no statistically significant difference was found in the mean serum levels of FSH in the two groups after drilling.

In a study comparing ULOD and BLOD with fixed energy dose (600 J/ovary) regardless ovarian volume, the authors found that no significant difference between the two groups as regards ovulation rate (60 vs. 64.4%), spontaneous menstrual cycles (66.1 vs. 71.1%) and conception rates (33.1 vs. 40%). In contrast, patients of both groups showed reduction in the serum levels of LH and testosterone, but without a significant difference between both groups. No significant change was found in the mean serum level of FSH in both groups ($p > 0.05$) [26].

Sunj et al. [9] showed that in CC-resistant PCOS patients undergoing BLOD with fixed thermal dose, the ovulation rate with larger right ovary was eight times higher than those with larger left ovary. But in patients undergone ULOD with adjusted thermal dose, there was no association between the received adjusted thermal dose by the more enlarged right ovary and the rate of ovulation, but there was a negative correlation between the received adjusted thermal dose by the smaller right ovary and the rate of ovulation.

Rezk et al. 2015 showed that ULOD using 60 Joules/cm3 applied to the larger ovary, while group II ($n = 53$) underwent BLOD with fixed doses of 1200 J. Ovulation and pregnancy rates at 3-month periods were comparable ($p > 0.05$), but was significantly higher in BLOD at 6-month period ($p < 0.05$). There was a highly significant difference between the two groups regarding the AMH level at 3- and 6-month follow-up periods ($p < 0.001$) with lower levels in the BLOD group. The AFC was comparable in the two groups after 3 months ($p > 0.05$) but became higher in the ULOD at 6-month follow-up period ($p < 0.001$) [16].

Menstrual cycle resumption in the thermal dose adjusted based on ovarian volume (60 J/cm^3) was higher than in CC-resistant PCOS patients with fixed dose (600 J per ovary).Also, there were higher ovulation (81.8 vs. 62.2%) and conception rates (51.7 vs. 36.8%) in CC-resistant patients with adjusted energy dose based on ovarian volume than in patients received fixed dose through 4 puncture technique [18].

Our study concluded that bilateral laparoscopic ovarian drilling with thermal dose adjusted according to ovarian volume is more effective than the right-sided unilateral technique with thermal dose adjusted according to ovarian volume in terms of menstrual cycle resumption, total ovulation and cumulative pregnancy rates in CC-resistant PCOS patients. Further studies on larger sample size and different population are needed to confirm our findings.

Compliance with Ethical Standards

Conflicts of interest There are no conflicts of interest

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Written informed consent obtained from all participants

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