Ovarian performance after laparoscopic ovarian drilling in women with polycystic ovary syndrome

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Abstract: Background: Polycystic ovary syndrome is considered the most common cause of anovulatory infertility. Laparoscopic ovarian drilling is an effective treatment for clomiphene citrate-resistant PCOS. Objectives: To evaluate ovarian performance after laparoscopic ovarian drilling assessed by comparison of antral follicle count and 3D power Doppler indices of ovarian stromal blood flow before and after the procedure. Design: A prospective study of women undergoing laparoscopic ovarian drilling as a treatment for clomiphene citrate-resistant PCOS. Ultrasound examination of antral follicle count (AFC) and 3D power Doppler indices of ovarian stromal blood flow was performed before and 6 months after the surgery. Setting: University teaching hospital. Patients: Thirty-five women with polycystic ovarian syndrome who failed to ovulate with clomiphene citrate and who subsequently underwent laparoscopic ovarian drilling and three-dimensional ultrasound examination. Main outcome measures: Regulation of menstrual pattern, ovulation rate, conception rate and changes in AFC and 3D power Doppler indices of ovarian stromal blood flow in non-pregnant women 6 months after the LOD. Results: Among 35 PCOS women with irregular menstrual pattern underwent LOD, 27 women had regular menstrual pattern after the procedure (77.14%). Ovulation rate was 74.29% (26/35), and the pregnancy rate was 31.43% (11/35). There were statistically significant differences between AFC and 3D power Doppler indices of ovarian stromal blood flow (FI, VI and FVI) before and after LOD as p values were <0.001, <0.001, <0.001 and <0.001 respectively.
Conclusion: LOD significantly improves menstrual pattern, ovulation rate and pregnancy rate in clomiphene citrate-resistant PCOS. It also decreases values of AFC and 3D power Doppler indices of ovarian stromal blood flow as an evidence of normalization of ovarian functions. Measuring these values in women with anovulatory PCOS undergoing LOD may provide a useful tool in evaluating the outcome of LOD.
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1. Introduction

Polycystic ovary syndrome is the most common reproductive endocrinopathy affecting up to 18% of reproductive-aged women worldwide **(1).** PCOS is the most common cause of anovulatory infertility with approximately 90% of women, attending infertility clinics for anovulation, are affected by PCOS **(2)**. Polycystic ovary syndrome is a heterogeneous syndrome of clinical and/or biochemical androgen excess, ovulatory dysfunction and polycystic ovaries (PCO). Women with PCOS are at increased risk of reproductive abnormalities **(3)**. Also, PCOS is suggested to have a genetic origin **(4,5)**. ESHRE/ASRM PCOS consensus workshop has been carried out in Rotterdam in 2003 and looked at diagnostic criteria for PCOS **(6)**. The Rotterdam diagnostic consensus included at least two of the following three criteria: oligo ovulation or anovulation, clinical and/or biochemical evidence of hyperandrogenism, and ultrasonographic features of polycystic ovaries, with the exclusion of medical conditions such as congenital adrenal hyperplasia, androgen-secreting tumors, or Cushing's syndrome **(7)**.

Laparoscopic ovarian drilling is widely accepted as the second-line treatment of PCOS after the failure of clomiphene citrate treatment. Some authors stated that the beneficial effect of LOD is rather transient whereas others appear to indicate that the treatment may have a long-term beneficial effect **(8)**. While the exact mechanism of action of LOD in PCOS is unclear, it was suggested that the partial destruction of some ovarian follicles and stroma might result in a local and systemic reduction of androgens and inhibin levels followed by increased FSH levels, promoting follicular maturation and subsequent ovulation gonadotropins **(9)**.

The antral follicle count (AFC) is a direct quantitative marker of ovarian reserve and responsiveness **(10)**. It was showed that there is a significant increase in ovarian stromal peak systolic blood flow velocity and time-averaged maximum velocity in women with PCOS over that of healthy women **(7)**. Power Doppler ultrasound is more sensitive than color Doppler imaging at detecting low-

velocity flow, so it provides improved visualization of small vessels in ovarian stroma **(11)**.

The aim of the current study is to evaluate ovarian performance after laparoscopic ovarian drilling in women with clomiphene citrate-resistant PCOS through assessment of changes in antral follicle count (AFC) and ovarian stromal blood flow before and after LOD using 3D power Doppler ultrasonography.

2. Materials and methods

A prospective interventional clinical study included 35 infertile anovulatory women with clomiphene citrate-resistant PCOS who underwent LOD, between November 2015 to April 2017, and all enrolled women were recruited from the attendants of the Outpatient Clinic and Endoscopy Unit in Al-Azhar University Hospitals. The study was approved by the Local Ethics Committee for Research. All women were informed about the study and a detailed written informed consent was taken from all participants before being included in the study. All women included in this study aged between 18-35 years with body mass index (BMI) between 20-30 k/m2, study subjects were with primary anovulatory infertility for one year or more. All women included should have normal hysterosalpingography (HSG) and their partners should have normal semen analysis according to the 2010 WHO criteria **(12)**. PCO was diagnosed according to the 2003 ESHRE/ASRM (Rotterdam) criteria **(6)**. Clomiphene citrate resistance was defined as failure to ovulate after CC administration up to a daily dose of 150 mg from cycle days 2–6 for at least three consecutive cycles **(13)**. The exclusion criteria were: Age was <18 or >35 years, tubal or male factor infertility, previous use of metformin, women with organic pelvic pathology as endometriosis at laparoscopy, previous history of ovarian surgery, history of diabetes mellitus or thyroid disease and PCOS-like conditions as Cushing's syndrome.

All women enrolled in this study were subjected to full detailed history either medical, surgical, past history, obstetric history or sexual history with a special stress on the menstrual pattern, fertility status, any previous investigations or treatment given to the patient for PCOS. General and local examinations were performed. General examination was done with a particular stress on anthropometric measurements and clinical manifestations of hyperandrogenism. On day three of the normal cycle or after progestin-induced menstruation; anthropometric measurements were obtained from all women of all three groups. The hormonal assay was obtained at early follicular phase (day 3) of the cycle before LOD and included FSH, LH, Prolactin, Estradiol, AMH and Testosterone.

Ultrasound examinations were performed using three-dimensional (3D) transvaginal 7.5-MHz power Doppler ultrasound to assess the ovarian volume, morphology, the total antral follicle number in both ovaries (measuring 2–9 mm), and to monitor the evidence of ovulation at each visit to the clinic after the LOD **(14,15)**. Power Doppler measurements were performed in the early follicular phase before LOD and repeated in the early follicular phase of the cycle at 6-month follow-up. Three indices quantifying the power Doppler signal were determined: vascularization index (VI), flow index (FI), and vascularization flow index (VFI). The total Antral follicle count (AFC) defined as the count of all antral follicles measuring 2–10 mm in both ovaries at the baseline examination session. Ultrasonographic examination was repeated monthly for 6 months' follow-up period.

The same experienced operator performed the laparoscopic procedures during the early post-menstrual phase (spontaneous or withdrawn). The routine tubal patency testing with methylene blue was done for all patients followed by ovarian drilling. Then, the technique of ovarian drilling was done according to the technique described by Amer et al. **(16)**. Duration of surgical procedure, blood loss, and hospital stay were recorded. All Intra- and postoperative complications were carefully recorded for each group. Based on clinical conditions, patients were discharged either on the same day of the surgical procedure or one day postoperatively.

All Patients were followed up until they successfully conceived or for up to 6 month period. The main outcome measures included menstrual pattern, ovulation rate, pregnancy rate and the sonographic features (AFC and 3D power Doppler indices of ovarian stromal blood flow). Follicular monitoring was evaluated by transvaginal U/S measurements. The scans were performed by the same experienced examiner at the three-day interval, starting on day 7 (during the first month after surgery), and subsequently on the second day after the onset of menses. When the follicular dimensions achieved at least 16 mm, the TVS started to be performed daily. The day of ovulation had been defined retrospectively with the observation of follicular collapse and of the appearance of free fluid in the cul-de-sac. Pregnancy was diagnosed by positive quantitative of b-hCG serum level (more than 50 IU/ml or a rising titer is diagnostic as well) and the appearance of a gestational sac by transvaginal ultrasound examination.

Statistical analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) v20.0. Quantitative data were expressed as the mean± standard deviation (SD). Qualitative data were expressed as frequency and

percentage. P-value <0.05 was considered significant, <0.001 was considered as highly significant and >0.05 was considered insignificant.

3. Results

Participants in the study had a higher level of AMH, testosterone and LH/FSH ratio than normal population (Table 1). Also, they had higher AFC and 3D power Doppler indices of stromal blood flow than of that of the normal population (table2). Regulation of menstrual pattern after LOD occurred in (27/35) of the included PCOS women. Ovulation rate was 74.29% while pregnancy rate was 31.43% in 6 months' follow-up period after LOD (figure 1). Further analysis revealed that (23/26) of women who ovulated after LOD also had a regular menstrual pattern (88.5%). Also, the analysis showed that there is no significant relation between the preoperative levels of the hormonal profile of the participants (FSH, LH, prolactin and AMH) and spontaneous pregnancy after LOD. However; there was a significant relation between preoperative testosterone level and spontaneous pregnancy after LOD (Table 3).

After LOD, there was a significant reduction in AFC and the ovarian stromal power Doppler flow indices at 6 months' follow-up period (Table 4) (figure 1). Also, no relation was revealed between preoperative AFC and 3D power Doppler indices values and spontaneous pregnancy after LOD.

Table (1): Clinical and hormonal study of enrolled women with PCOS.

Descriptive data	**Range**	**Mean±SD**
Age (years)	22-34	28.40±3.54
BMI kg/m2	20.4-30	26.71±2.50
FSH IU/L	3.6-8.6	6.08±1.41
LH IU/L	7.4-20.8	13.65±2.58
Prolactin ng/ml	5.8-18.7	12.13±3.74
E2 pg/ml	40.7-88.45	65.53±11.27
AMH ng/ml	3.3-9.3	5.78±1.51
Testosterone (nmol/l)	1.3-5.3	3.98±1.13

Table (2): Basal ultrasonographic features of the study group before the LOD.

Descriptive data	**Range**	**Mean±SD**
AFC	20-28	23.20±2.62
FI	46.9-57.3	51.49±2.99
VI	3.7-6.1	4.89±0.67
FVI	2.56-3.1	2.86±0.13

AFC: Antral follicle count, FI: Flow index, VI: Vascularization index and FVI: Flow-vascularization index.

Table (3): Relation of pregnancy occurrence as an outcome to pre-operative laboratory investigations.

	Outcome		**p-value**
	Pregnant	**Not Pregnant**	
	Mean±SD	**Mean±SD**	
FSH IU/L	6.24±1.28	6.01±1.48	0.666
LH IU/L	12.86±2.87	14.02±2.42	0.223
Prolactin ng/ml	10.98±3.32	12.65±3.87	0.223
E2 pg/ml	65.11±9.75	65.72±12.09	0.885
AMH ng/ml	5.68±1.83	5.82±1.38	0.805
Testosterone nmol/l	3.39±1.23	4.25±0.99	0.035

Table (4): Comparison between AFC, FI, VI and FVI before and after laparoscopic ovarian drilling (DOL) in non-pregnant subjects.

	Before	**After**	**Mean Diff.**	**p-value***
AFC	22.96±2.66	14.38±2.20	8.58	**<0.001**
FI	51.57±2.84	43.85±2.52	7.72	**<0.001**
VI	4.87±0.68	2.56±0.53	2.31	**<0.001**
FVI	2.88±0.11	1.65±0.26	1.23	**<0.001**

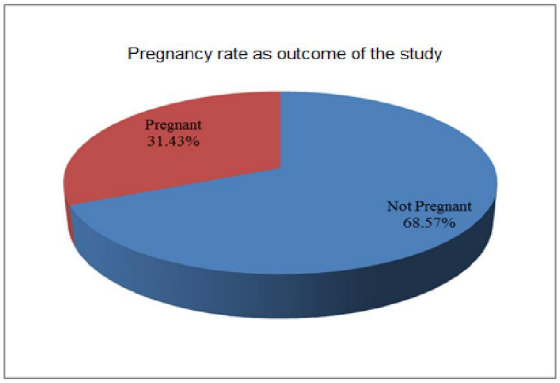

Figure (1): Pie chart figures occurrences of pregnancy after LOD as an outcome of the study.

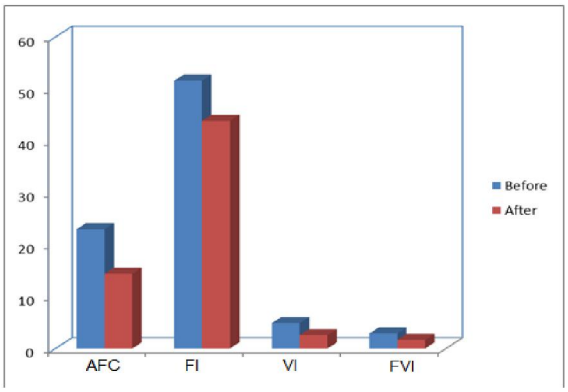

Figure (2): Bar chart shows the difference between AFC, FI, VI and FVI before and after laparoscopic ovarian drilling (LOD) in non-pregnant subjects.

4. Discussion

The aim of the present study is to evaluate the effects of laparoscopic ovarian drilling on the ovarian performance assessed by ultrasonographic changes in women with polycystic ovary syndrome, specifically total antral follicle count (AFC) and three-dimensional power Doppler indices of ovarian stromal blood flow. All patients were followed up after treatments until they conceived or for up to a period of 6 months.

In the present study, among 35 women diagnosed with PCOS and all had the irregular menstrual pattern and anovulatory primary infertility, 27 of them menstruated regularly after LOD (77.14%) while 8 still had an irregular menstrual pattern (22.86%). These results agree with previous studies described success and utility of this procedure in treating PCOS. They reported improvement of the menstrual pattern after LOD and the rate of regulation of the menstrual pattern ranged from 67% to 76% after LOD. (**16**,**17**,**18**,**19**). A possible explanation of improvement of the menstrual pattern after LOD is that LOD improves ovulation rate and this, in turn, regulates the menstrual cycle as the cause of oligomenorrhea observed in PCOS patients is anovulation **(20)**. This is evidenced by our results as of 26 patients ovulated regularly after LOD, 23 of them had a regular menstrual cycle (88.5%) while 4 patients menstruated regularly of 9 women showed no evidence of ovulation after the procedure (44.4%). The previous study also had similar results as 95.1% of patients who ovulated after LOD had a regular menstrual cycle while only 46.4% of patients, who did not ovulate, had a regular cycle **(19)**.

The present study, the ovulation rate after LOD was 74.29% (26 of 35 women have PCOS with anovulation). The ovulation was confirmed by ultrasound follow-up every cycle after LOD in the 6 months follow-up period. Ovulation was diagnosed by follicular enlargement followed by collapse. Also, the spontaneous pregnancy rate was about 31.43% (11 of 35 women with anovulatory primary infertility). Ovulation and pregnancy rates have a wide range of studies assessed the effect of LOD on both. Some studies reported a relatively high ovulation and pregnancy rates after LOD while others did not. Ovulation rate ranged from 83% to 90% while pregnancy rate ranged from 47% to 73% in some studies which confirmed relatively high ovulation and pregnancy rates after LOD **(18,21,22,23,24)**. Other studies reported a lower ovulation rate and, consequently, a lower pregnancy rate. They reported ovulation rate ranges from 47% to 54% and pregnancy rate ranges from 21% to 28% **(25,26,27)**. The explanation of this relatively significant difference between the results of the previous studies is the possible presence of other factors that may also cause infertility such as unrecognizable male infertility or tubal pathology which may reduce the success rate of LOD. Another explanation is the restrict condition of clomiphene resistance in the studies had relatively lower ovulation and pregnancy rate **(26)**. In our study 24 of 35 women with PCOS failed to conceive after LOD (68.57%) despite high ovulation rate (74.29%). The explanation of that is the amount of stromal tissue destructed by LOD was not enough to induce the favorable changes responsible for the improvement of reproductive outcome or presence of another undetected reason for infertility such as immune related infertility **(26)**.

We found a relation between ovulation after LOD and occurrence of spontaneous pregnancy. Of 26 patients in our study who ovulated regularly, 11 got pregnant (42%) while of 9 did not ovulate; no patient got pregnant (0%). These results agree with previous studies **(19)**. Our study also did not show any significant difference between patients who got pregnant and patients who did not in relation to body mass index (BMI) before the LOD which is antagonized with previous studies **(28)**. This controversy may be due to our exclusion of patients

whose BMI is over 30 k/m2. Also, we did not find a relation between preoperative hormonal assay levels (FSH, LH, estradiol and AMH) and spontaneous pregnancy after LOD. Some previous studies showed that there is a relation between preoperative LH level and ovulation after LOD rather than spontaneous pregnancy (**17**,**29**). These conflicting results may be due to our small sized study. Also, the previous studies found a statistically significant relation between pre-operative LH value and occurrence of pregnancy with cut-off value about 12 IU/L. above this value, they found a better reproductive outcome. In our study, LH values in patients who got pregnant and patients who did not be 12.86±2.87 IU/L and 14.02±2.42 IU/L respectively. So, both were above the cut-off value concluded by the other study **(29)**. As regard estradiol level preoperatively, previous studies agreed with our results. However; they used ovulation as a reproductive outcome rather than pregnancy **(17)**.

About AMH, our study disagreed with many previous studies confirmed the positive relation between preoperative AMH and reproductive outcome after LOD **(16,17,30)**. These conflicting results may be explained by the small sample size of our study (n = 35). Also, we used pregnancy as reproductive outcome while others used ovulation. The previous studies also used LOD as first-line treatment for PCOS rather than second-line treatment **(16)**.

There was a significant relation between pre-operative Testosterone and pregnancy after LOD as an outcome. This comes in line with previous studies **(17,31)** while antagonizes others **(23,30,32)**. The possible explanation for the disagreement of these studies could be due to the relatively small sample size of the studied groups in the antagonizing studies. The present study also showed no significant relation between preoperative AFC and 3D power Doppler indices of ovarian stromal blood flow and spontaneous pregnancy as a reproductive outcome after LOD. In connection with AFC, our results come in line with our previous results in relation to preoperative AMH as there is a strong correlation between follicle number and serum AMH levels as demonstrated by some authors **(15)**, suggesting that the increased AMH levels in PCOS are associated with early antral follicles **(33)**. Previous studies also found no significant relation between preoperative 3D power Doppler indices of ovarian stromal blood flow and reproductive outcome after LOD **(30)**.

Our study also found that AFC was decreased significantly after LOD. Previous studies also showed same results **(17,30,34,35)**. It has been accepted that AFC may be a good quantitative predictor of the ovarian reserve. The number of antral follicles, which is closely related to reproductive age, could substantially reflect the number of remaining primordial follicles. Therefore, on the one hand, LOD should have some diathermal effect on the ovarian tissue leading to a decrease in AFC and the ovarian reserve. Importantly, on the other hand, the ovarian reserve in PCOS women undergoing LOD remains high **(36)**. Regarding the three-dimensional power Doppler indices, we found a statistically significant decrease of flow index (FI), vascularization index (VI) and flow vascularization index (FVI) after LOD. These results agreed with some previous studies **(14,30,35)**. Other studies revealed increased vascularization after LOD **(37)**. These conflicting results may be explained by the fact that many of these studies have limited power because of small sample sizes and open inclusion/exclusion criteria that led to the recruitment of inappropriate controls. In addition, different criteria for the diagnosis of PCOS, variable Doppler settings and inconsistencies in the phase of the cycle when the examinations were conducted; all of that are possible explanations. Also, previous studies found that ovarian blood flow decreased after LOD using 2D ultrasound to assess resistance index (RI) and pulsatility index (PI) after LOD **(38,39)**.

A shortcoming of the present study is its small sample size and thus making it underpowered. Also, lack control group of healthy individuals to compare with the PCOS patients making it impossible to determine if the parameters included in this study could be used for evaluation of PCOS or not. In conclusion, LOD improves menstrual pattern, ovulation rate, and pregnancy rates. Also, antral follicle count and 3D power Doppler indices of stromal blood flow reduced after LOD and their measurement before and after LOD may provide useful tools for evaluating the outcome of LOD.

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