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Impact of Laparoscopic Ovarian Drilling (LOD) on Ovarian Reserve and Ovarian Stromal Blood Flow Using Two-Dimensional (2D) Power Doppler in Anovulatory Women with Polycystic Ovary Syndrome (PCOS)

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ABSTRACT

Aim of the Study: this study aimed to determine the effect of LOD on ovarian reserve and ovarian stromal blood flow changes, by using Two-Dimensional (2D) Power Doppler Ultrasongraphy in anovulatory women with Polycystic Ovary Syndrome (PCOS) and whether this could explain the mechanism of action of LOD. **Patients and methods**: this study was conducted in the Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Al-Hussein University Hospital, El-Sayed Galal Hospital and EL-Sheikh Zayed Especialized Hospital in the period between November 2016 and February 2018. This study included 30 anovulatory polycystic ovary women with clomiphene citrate (CC)-resistant and 30 fertile women as the control group. Laparoscopic ovarian drilling was done. Serum levels of hormonal profile were measured (AMH, LH, FSH, LH/FSH ratio and total testosterone), ovarian stromal blood flow Doppler indices (RI and PI) and occurrence of ovulation or pregnancy. **Result:** in this study we reported our findings regarding the effects of LOD on AMH, hormonal profile and ovarian stromal blood flow in women with PCOS with clomiphene resistance. These results suggested that the measurement of AMH, LH, LH/FSH ratio, total testosterone, ovarian volume and ovarian stromal blood flow by Doppler were in discrimination of PCOS from potentially normal women. The data in our study suggested that there were no significant differences as regard AMH, hormonal profile except total testosterone, ultrasound ovarian findings and ovarian stromal blood flow before and after LOD, but there were significant differences as regard total testosterone before and after LOD. Also, there was good predictive value for AMH after LOD for ovulation and clinical pregnancy.

Conclusion: measuring AMH for anovulatory women with PCOS undergoing LOD may be a useful tool in evaluating the outcome of LOD, but ovarian stromal blood flow 2D Doppler indices did not show significant changes predicting ovulation or pregnancy rate after LOD.

Keywords: polycystic ovary syndrome, laparoscopic ovarian drilling, ovulation, anti-Mullerian hormone, ovarian stromal blood flow.

INTRODUCTION

Polycystic ovary syndrome (PCOS), one of the most common endocrine disorders in women of childbearing age, is characterized by marked increase in preantral follicle number arranged peripherally around a dense core of stroma or scattered throughout an increased amount of stroma [(1)]. This is coupled with menstrual disturbance, hyperandrogenism, and anovulation [(2)].

Ovarian reserve is related to the size, number and quality of oocytes within follicles. The ovarian reserve is the reproductive ability of ovary that shows number of follicles in it. Aging decreases ovarian reserve and subsequently reproductive ability of women [(3)].To assess ovarian reserve **Gleicher *et al.*** [(4)] measured serum level of FSH and E2 in the follicular phase. One of the best ovarian reserve determining factors is antral follicle count which is assessed by transvaginal ultrasound tests during the follicular phase. Within the last years, serum AMH measurement has been introduced as one of the best and easiest markers of ovarian reserve [(5)].Ovarian stromal peak systolic blood flow velocity and time averaged maximum velocity were found to be significantly greater in women with PCOS than in infertile women with healthy ovaries [(6)]. Power Doppler ultrasound is more sensitive than Color Doppler imaging at detecting low velocity flow, thus it overcomes the angle dependence of standard color Doppler and provides improved visualization of small vessels [(7)].

Anti-Müllerian hormone (AMH) is a dimeric glycoprotein, which is a member of the transforming growth factor family ß (TGF-ß). In the female, AMH is secreted exclusively by granulosa cells of primary, pre-antral and small antral follicles (4-6mm) [(8)]. Its secretion gradually diminishes in the subsequent stages of follicle development and is practically undetectable in follicles (8 mm) [(8)]. Serum AMH concentrations have been correlated with the number of small follicles and hence ovarian reserve. The size of the pool of small follicles remains relatively constant during the menstrual cycle and consequently circulating

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AMH concentrations show minimal fluctuation throughout the menstrual cycle. AMH gradually falls with advancing age owing to a depletion of the number of follicles as menopause approaches [9].Laparoscopic Ovarian Drilling (LOD) (Ovarian Diathermy) is widely used to induce ovulation in PCOS patients. However 30% of patients do not respond to laparoscopic treatment due to an unknown reason. LOD destroys parts of the ovaries and this surgery is not commonly used, however it can be used as an alternative option for infertile women who are still not ovulating in terms of lack of response to the drug [10].Identifying factors that determine the response of women with PCOS to LOD will help in selecting patients who are likely to benefit from this treatment, thus avoiding fruitless treatment and improving success rates. In a previous study, we have reported on factors affecting the success of LOD [11]. Laparoscopy can lead to injuries in ovarian tissue and induce the reduction of ovarian reserve. The extent of damage that affects ovarian reserve correlates with the content of ovarian tissue removed during surgery and the damage to the ovarian vascular system during laparoscopy [10].

AIM OF THE WORK

This study aimed to determine the effect of LOD on ovarian reserve and ovarian stromal blood flow changes, by using Two-Dimensional (2D) Power Doppler Ultrasongraphy in anovulatory women with PCOS and whether this could explain the mechanism of action of LOD.

PATIENTS AND METHODS

Patients

This study was conducted in the Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Al-Hussein University Hospital, El-Sayed Galal Hospital and EL-Sheikh Zayed Especialized Hospital in the period between November 2016 and February 2018. It included 30 anovulatory PCOS women with CC-resistant undergoing LOD (PCOS group) and 30 fertile women with a regular menstrual cycle and normal ovaries (by ultrasound examination) as the control group. **The study was approved by the Ethics Board of Al-Azhar University.**

Inclusion criteria:

1- Patient's ages 18 to 35 years.

2- All patients were anovulatory with PCOS according to Rotterdam criteria, 2003 (two criteria are sufficient for diagnosis of PCOS: (i) oligo- and/or an-ovulation; which is manifested clinically by secondary amenorrhoea or oligomenorrhoea, (ii) hyperandrogenism (clinical and/or biochemical); (hirsutism and/or elevated serum level of total testosterone), (iii) polycystic ovaries (should be present in all cases) by ultrasonography (each ovary contains 12 or more follicles measuring 2–9 mm and/ or ovarian volume more than 10 ml), and patient were also Clomiphene citrate resistance.

3- Clomiphene citrate resistance is 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.

4- Body mass index (BMI):from25-30 i.e. over weight.

Exclusion criteria

- Age below 18 years or more than 35 years
- Women with single ovary; previous ovarian cystectomy.
- Any diseases at affecting the ovarian environment and/or function (including endometriosis and leiomyomas).
- Tubal or male factor infertility.
- Associated medical conditions e.g. Thyroid disease, hyperprolactinaemia, diabetes, cardic disease, renal disease…etc.

Type of study:

Prospective controlled clinical study.

Ethical considerations:

The study protocol was approved by the local Ethical Committee of Faculty of Medicine, Azhar University. An informed written consent was taken from all patients and their husbands before starting the study and every patient had the right to leave the study at any time.

Methods

The following was done:

1- Full detailed history:

A full detailed history was taken from all patients:

- Personal history*:* name, age, residence, occupation, duration of marriage, number of living children, previous marriage, and special habits of medical importance such as smoking and alcohol intake.
- Present history for analysis of infertility (type and duration of infertility).
- Menstrual history: age of menarche, cycle regularity, amount and duration of menstrual bleeding, dysmenorrhea, intermenstrual bleeding or discharge, symptoms of premenstrual tension syndrome, 1st day of last normal menstrual period (amenorrhea or oligomenorrhea).

- Obstetric history: parity, number of children, mode of each delivery, and outcome of each pregnancy and pueperium.
- Past history of: a) Diseases such as hypertension, cardiac diseases, thyroid diseases or chronic lung disease; b) Drugs e.g. Clomiphene Citrate, human chorionic gonadotrophin (HCG); c) Operations such as previous tubal or ovarian surgery; d) History of drug allergy.
- Family history: of chronic medical disorders such as diabetes mellitus, hypertension.
- Contraceptive history.

2- **General examination:**

- Weight, height, and body mass index (BMI).
- Blood pressure, pulse, temperature, and respiratory rate.
- Neck examination for thyroid enlargement, lymph nodes, congested neck veins and acanthosis nigricans.
- Face examination for acne, hirsutism and cushinoid facies.
- Eye examination for pallor, jaundice and exophthalmos.
- Chest examination for heart, lung and breast examination to exclude galactorrhea.
- Secondary sexual characters and fat distribution.
- Manifestations of hyperandrogenism or virilism such as pattern of distribution of hair in different body areas (degree of hirsutism) in the area of the moustache, beard, sideburns, chest, buttocks, inner thighs, back ets….), acne, oily skin, change in voice (hoarseness of voice), decreased breast size, male-pattern baldness or hair thinning and increased muscle mass.

3- **Abdominal examination:** was done detect large hernia, palpable abdominal masses or organs, hair distribution, red striae and scars of previous operation.

4- **Local examination:**

Local genital examination was done to exclude any abnormalities in the genital tract

5- **Ultrasound:**

Transabdominal and/or transvaginal ultrasound was done to exclude patients with ovarian masses or pelvi-abdominal masses. Other investigations were done to fulfill the inclusion and exclusion criteria (Serum prolactin level, free T3, free T4, TSH).

6- **Hormonal profile:**

Serum levels of AMH, LH, FSH and total testosterone were measured in the early follicular phase (days 2-4 of spontaneous cycle in oligomenorrhic patients). To start the study in amenorrhic patients (after exclusion of pregnancy) they received progesterone (oral Norethisterone Acetate 10 mg daily for 5 days) to induce withdrawal bleeding and hormonal profile was measured in days 2-4 of this withdrawal bleeding.

7- **Doppler study before LOD*:***

Ultrasound examinations were performed using transvaginal 7.5-MHz power Doppler ultrasound (Philips ClearVue 350 ultrasound system, USA). While the patients at lithotomy position after they had evacuated their urinary bladder and on the same days of the hormonal assay, 2D TVS was used to examine the uterus for any abnormality and measuring the uterine size and endometrial thickness and then to identify PCO criteria in both ovaries and to measure ovarian volume, ovarian stromal blood flow. Pulsatility index (PI) and resistance index (RI) were calculated.

8- **Laparoscopic ovarian drilling:**

Pre-operative preparation was done to exclude patients with contraindications to general anesthesia or laparoscopic surgery:

- Full investigation e.g. CBC, FBS, kidney function tests, liver function tests, PT, PTT, INR, ECG, chest X-ray.
- Bowel preparation.
- Fasting for at least 8 hours.
- Pregnancy test immediately before the procedure.

Follow up

1 -Hormonal assay (AMH - FSH - LH - total testosterone) was performed in the early follicular phase (days 2-4 of the menstrual cycle) of the first post-operative spontaneous menstruation (which occurred within 6 – 8 weeks after the operation). In non-menstruating patients, hormonal assay (AMH - FSH - LH - total testosterone) was performed by the end of the 8 weeks.

2- Blood flow assessment (PI - RI) was performed in the early follicular phase (days 2-4 of the menstrual cycle) of the first post-operative spontaneous menstruation (which occurred within 8 weeks after the operation). In non-menstruating patients, the blood flow assessment was performed by the end of the 8 weeks.

3- In menstruating patients, this cycle was monitored to assess hormonal profile, ovarian stromal blood flow Doppler parameters and finally to detect ovulation.

4- Ovulation was assessed by serial transvaginal ultrasound until visualization of pre-ovulatory follicle of at least 18 mm. Ovulation was confirmed by seeing follicle collapse on subsequent transvaginal ultrasound, appearance of fluid in the Cul-de-sac and elevated mid-luteal serum

progesterone level > 5 ng/ml. Ovulating group was informed to report the occurrence of natural conception for 6 months after LOD.

5- Patients who did not menstruate (pregnancy should be excluded at first) or did not ovulate within 8 weeks after drilling as evidenced by poor or no follicular growth by serial transvaginal ultrasound folliculometry, and low mid-luteal serum progesterone level < 5 ng/ml were referred to be re-evaluated.

Statistical analysis

Correlation coefficient (Pearson r)	Strength of correlation
<.2	Very weak
.2 –.39	Weak
.4 –.59	Moderate
.6 –.79	Strong
.8 – 1	Very strong

Receiver-operating characteristic (ROC) curve analysis was used to examine the predictive value of ovarian volume, AMH or ovarian Doppler indices. The area under the ROC curves (AUC) was interpreted as follows:

Area under ROC curve (AUC)	Diagnostic / predictive value
.9 – 1.0	Excellent
.8 –.89	Good
.7 –.79	Fair
.6 –.69	Poor
<.6	Fail

P-value <0.05 was considered statistically significant.

RESULTS

I- Patients clinical characteristics:

Mean age (± SD) of control patients was 27.1 ± 5.4 years while in PCO patients, it was 25.9 ± 4.8 years ranging between 18 and 35 years. There was a non-significant difference between the two groups as regard age (p. value 0.457).

Mean age at menarche (± SD) of control patients was 13.4 ± 1.1 years while in PCOS patients; it was 13.2 ± 1.2 years ranging between 11 and 15 years.

There was a non-significant difference between the two groups as regard age (p. value 0.591). Mean BMI (± SD) of control patients was 27.4 ± 1.5 kg/m^2 while in PCOS patients, it was 27.3 ± 1.4 kg/m^2 ranging between 25 and 30 kg/m^2. There was a non-significant difference between the two groups as regard BMI (p. value 0.72). This is shown in table (8).

Data were analyzed using Stata® version 14.2 (StataCorp LLC, College Station, TX, USA) and MedCalc© version 14.8 (MedCalc© Software bvba, Ostend, Belgium). Numerical variables were presented as mean and standard deviation (SD) and intergroup differences between PCO group and the control group were compared using the independent-samples t test. Paired numerical data in the study group before and after LOD were compared using the paired t test.

Correlations were tested using the Pearson product-moment correlation. The correlation coefficient (Pearson r) was interpreted as follows:

Table 1: comparison of PCOS and the control groups as regards demographic data

	PCOS group (n=30)		Control group (n=30)		
Variable	**Mean**	**SD**	**Mean**	**SD**	**p-value***
Age (years)	25.9	4.8	27.1	5.4	0.457
Age at menarche (years)	13.2	1.2	13.4	1.1	0.591
BMI (kg/m^2)	27.3	1.4	27.4	1.5	0.720

Data are mean and standard deviation (SD).
*Unpaired t test.

II- Hormonal assay comparison between PCOS group and the control group:

Serum levels of AMH, LH, FSH and total testosterone were measured in the early follicular phase days 2-4 of the spontaneous menstrual cycle or withdrawal bleeding in the PCOS group and in the early follicular phase days 2-4 of the spontaneous menstrual cycle of the control group and the results in both groups were compared together.

In **table 1**, there was:

1- A significant difference between PCOS group and control group as regard AMH (P. value <0.001), LH (P. value <0.001), LH/FSH ratio (P. value 0.003) and Testosteron (P. value <0.001).

2- A non-significant difference between PCOS group and control group as regard FSH (P. value 0.800).

Table 2: comparison of PCOS and the control groups as regards hormonal profile

	PCOS group (n=30)		Control group (n=30)		
Variable	**Mean**	**SD**	**Mean**	**SD**	**p-value***
AMH (ng/ml)	6.2	1.5	2.9	0.6	**<0.001**
FSH (IU/l)	4.4	1.4	4.2	2.6	0.800
LH (IU/l)	12.7	3.2	5.5	3.6	**<0.001**
LH/FSH ratio	3.47	1.48	1.91	1.74	**0.003**
Testosterone (nmol/l)	3.4	1.0	1.5	0.5	**<0.001**

Data are mean and standard deviation (SD).
*Unpaired t test.

III- Doppler and ultrasound findings in PCOS group and the control group:

Ovarian Volume, Antral Follicular Count and Ovarian stromal blood flow indices (pulsatility index (PI) and resistance index (RI)) were measured in the early follicular (days 2-4 of the spontaneous menstrual cycle or withdrawal bleeding in PCOS group and in the early follicular phase days 2-4 of the spontaneous menstrual cycle of the control group. Both right and left ovaries were observed and analyzed in each patient and average ovarian volume and sum ovarian volumes as well as average Doppler parameters of ovarian stromal arteries were taken. Therefore, the mean values for all parameters of both ovaries were calculated and used in the statistical analysis.

In table 2:

1- There a was significant difference between PCOS group and control group as regard AFC (P. value <0.001), Average ovarian volume (P. value <0.001) and Total (Sum) ovarian volume (P. value <0.001).
2- there was significant difference between PCOS group and control group as regard Doppler indices presented in Average ovarian RI (P. value <0.001) and Average ovarian PI (P. value <0.001).

Table 3: comparison of PCOS and the control groups as regards U/S and Doppler findings

	PCOS group (n=30)		*Control group (n=30)*		
Variable	**Mean**	**SD**	**Mean**	**SD**	**p-value***
Right ovarian volume (ml)	11.8	2.2	9.9	2.1	**0.006**
Left ovarian volume (ml)	12.0	2.4	9.5	2.1	**0.001**
Average ovarian volume (ml)	11.9	1.4	9.7	1.2	**<0.001**
Total (Sum) ovarian volume (ml)	23.8	2.8	19.4	2.3	**<0.001**
AFC	52	12	17	6	**<0.001**
Right ovarian RI	0.81	0.07	0.86	0.07	**0.027**
Left ovarian RI	0.76	0.07	0.88	0.07	**<0.001**
Average ovarian RI	0.79	0.05	0.87	0.05	**<0.001**
Right ovarian PI	2.45	0.62	3.31	0.99	**0.002**
Left ovarian PI	2.12	0.62	3.34	0.73	**<0.001**
Average ovarian PI	2.28	0.40	3.32	0.65	**<0.001**

Data are mean and standard deviation (SD). *Unpaired t test.

Table 4: receiver-operating characteristic (ROC) curve analysis for discrimination between PCOS patients and controls using total (Sum) ovarian volume, ovarian RI, ovarian PI, AMH or testosterone

	Predictor				
ROC parameter	**Total ovarian volume**	**Average ovarian RI**	**Average ovarian PI**	**AMH**	**Testosterone**
AUC	0.889	0.865	0.891	1.000	0.987
SE	0.050	0.055	0.058	0.000	0.012
95% CI	0.756 to 0.964	0.726 to 0.950	0.759 to 0.966	0.918 to 1.000	0.894 to 1.000
z statistic	7.835	6.700	6.788	NA	42.394
p-value	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Youden index	0.650	0.600	0.757	1.000	0.913
Cut-off criterion	>19.1 ml	≤0.86	≤2.93	>3.97 ng/ml	>2.23 nmol/l

Sensitivity	100%	100%	95.7%	100%	91.3%
Specificity	65%	60%	80%	100%	100%

AUC, area under the ROC curve; SE, standard error; 95% CI, 95% confidence interval.
*DeLong method.

Table 4 showed the results of receiver-operating characteristic (ROC) curve analysis for discrimination between PCOS patients and controls using total ovarian volume, ovarian RI, ovarian PI, AMH or testosterone.Total (Sum) ovarian volume, average ovarian RI and average ovarian PI had good value for discrimination between PCOS patients and controls (AUCs = 0.889, 0.865 and 0.891, respectively). The best cut-offs were a total ovarian volume of >19.1 ml (sensitivity = 100%, specificity = 65%), an average ovarian RI of ≤0.86 (sensitivity = 100%, specificity = 60%) and an average ovarian PI of ≤2.93 (sensitivity = 95.7%, specificity = 80%).

AMH and testosterone had excellent diagnostic value (AUCs = 1.0 and 0.987, respectively). The best cut-offs were an AMH level of >3.97 ng/ml (sensitivity = 100%, specificity = 100%) and a testosterone level of >2.23 nmol/l (sensitivity = 91.3%, specificity = 60%).

Table 5: comparison of clinical, power Doppler and hormaonal measures before and after LOD in patients with PCOS

	Before LOD		***After LOD***		
Variable	**Mean**	**SD**	**Mean**	**SD**	**p-value***
BMI (kg/m^2)	27.3	1.4	27.4	1.4	0.803
Right ovarian volume (ml)	11.8	2.2	12.0	2.5	0.834
Left ovarian volume (ml)	12.0	2.4	13.7	3.1	0.061
Average ovarian volume (ml)	11.9	1.4	12.8	1.7	0.053
Total (Sum) ovarian volume (ml)	23.8	2.8	25.7	3.5	0.053
AFC	52	12	35	17	**0.001**
Right ovarian RI	0.81	0.07	0.83	0.07	0.561
Left ovarian RI	0.76	0.07	0.82	0.07	**0.013**
Average ovarian RI	0.79	0.05	0.82	0.05	**0.039**
Right ovarian PI	2.45	0.62	3.03	0.69	**0.010**
Left ovarian PI	2.12	0.62	3.00	0.56	**0.000**
Average ovarian PI	2.28	0.40	3.01	0.49	**<0.001**
AMH (ng/ml)	6.2	1.5	6.6	1.5	0.483
FSH (IU/l)	4.4	2.4	4.2	2.1	0.776
LH (IU/l)	12.7	3.2	11.6	2.8	0.273
LH/FSH ratio	3.5	1.5	3.7	2.6	0.702
Testosterone (nmol/l)	3.4	1.0	2.5	0.7	**0.003**

Data are mean and standard deviation (SD).
*Paired t test.

Table 5 showed comparison of clinical, power Doppler and hormonal measures before and after LOD in patients with PCOS and the following was found:

1- There was a statistical significant difference as regard AFC before and after LOD in the study group (P.value 0.001).
2- A statistical significant difference as regard Doppler Indices in the form of Average Ovarian RI and Average Ovarian PI before and after LOD in the study group (P.value was **0.039** and **<0.001** respectively).
3- A statistical significant difference as regard Testosterone before and after LOD in the study group (P.value was **0.003)**.
4- There was no statistical significant difference as regard Sum Ovarian Volume and AMH before and after LOD (P.value was **0.053** and **0.483** respectively).

Table 6: comparison of clinical, power Doppler and hormonal measures before and after LOD in patients with or without ovulation

	No ovulation (n=9)		Ovulation (n=21)		
Variable	**Mean**	**SD**	**Mean**	**SD**	**p-value***
Age (years)	27	7	26	4	0.690
Age at menarche (years)	14	1	13	1	0.085
Duration of infertility (years)	2.98	1.5	2.97	1.7	0.861
BMI before LOD (kg/m^2)	28.2	1.2	26.8	1.2	**0.024**
BMI after LOD (kg/m^2)	27.6	1.6	27.3	1.3	0.634
Average ovarian volume before LOD (ml)	11.7	1.6	12.0	1.4	0.627
Average ovarian volume after LOD (ml)	12.0	1.8	13.2	1.6	0.131
Total (Sum) ovarian volume before LOD (ml)	23.4	3.3	24.0	2.7	0.627
Total (Sum) ovarian volume after LOD (ml)	24.0	3.7	26.4	3.2	0.131
AFC before LOD	48	15	54	11	0.275
AFC after LOD	37	18	35	16	0.799
Average ovarian RI before LOD	0.78	0.06	0.79	0.05	0.571
Average ovarian RI after LOD	0.83	0.06	0.82	0.05	0.832
Average ovarian PI before LOD	2.21	0.22	2.31	0.46	0.584
Average ovarian PI after LOD	2.84	0.49	3.09	0.48	0.262
AMH before LOD (ng/ml)	5.5	1.3	6.5	1.6	0.153
AMH after LOD (ng/ml)	7.9	1.4	6.0	1.1	**0.002**
FSH before LOD (IU/l)	3.7	1.8	4.7	2.6	0.349
FSH after LOD (IU/l)	4.1	1.5	4.3	2.4	0.816
LH before LOD (IU/l)	12.1	2.7	12.9	3.5	0.617
LH after LOD (IU/l)	13.1	4.2	11.0	1.9	0.244
LH/FSH before LOD	3.8	1.4	3.3	1.5	0.524
LH/FSH after LOD	3.5	1.6	3.8	2.9	0.777
Testosterone before LOD (nmol/l)	3.3	1.2	3.5	0.9	0.625
Testosterone after LOD (nmol/l)	2.8	0.7	2.3	0.7	0.153

Data are mean and standard deviation (SD).
*Unpaired t test.

As regard occurrence of ovulation in menstruating patients; shows that:

1- 21 cases (70%) showed ovulation as evidenced by folliculometry (leading mean follicular diameter > 18 mm followed by seeing follicle collapse on subsequent transvaginal ultrasound, appearance of fluid in the Cul-de-sac) and elevated mid luteal serum progesterone level (> 5 ng/ml).
2- 9 Cases (30%) did not show ovulation as evidenced by poor or no follicular growth by serial transvaginal ultrasound folliculometry and low mid-luteal serum progesterone level (< 5 ng/ml).

In **table 6**, there was a statistical significant difference as regard BMI before LOD between Patients with Ovulation and Patients without Ovulation (*P.value* 0.024). Also there is a statistical significant difference as regard AMH after LOD between patients with ovulation and patients without o*vulation* (*P.value* 0.002).

Table 7: comparison of clinical, power Doppler and hormonal measures before and after LOD in patients with or without clinical pregnancy

	No clinical pregnancy (n=22)		Clinical pregnancy (n=8)		
Variable	**Mean**	**SD**	**Mean**	**SD**	**p-value***
Age (years)	26	5	25	3	0.709
Age at menarche (years)	13	1	13	1	0.139
BMI before LOD (kg/m^2)	27.3	1.4	27.1	1.4	0.745
BMI after LOD (kg/m^2)	27.5	1.5	26.9	1.1	0.359
Average ovarian volume before LOD (ml)	11.6	1.4	12.7	1.4	0.112
Average ovarian volume after LOD (ml)	12.9	1.6	12.8	2.2	0.888
Total (Sum) ovarian volume before LOD (ml)	23.3	2.7	25.4	2.8	0.112
Total (Sum) ovarian volume after LOD (ml)	25.8	3.3	25.5	4.3	0.888
AFC before LOD	53	12	50	14	0.543
AFC after LOD	33	18	42	12	0.191
Average ovarian RI before LOD	0.79	0.05	0.80	0.06	0.672
Average ovarian RI after LOD	0.83	0.05	0.82	0.04	0.652
Average ovarian PI before LOD	2.28	0.37	2.29	0.53	0.967
Average ovarian PI after LOD	3.05	0.52	2.90	0.39	0.521
AMH before LOD (ng/ml)	6.2	1.7	6.4	1.2	0.771
AMH after LOD (ng/ml)	6.9	1.4	5.5	1.1	**0.040**
FSH before LOD (IU/l)	4.1	2.1	5.4	3.1	0.256
FSH after LOD (IU/l)	4.4	2.2	3.7	1.7	0.534
LH before LOD (IU/l)	12.9	3.3	12.0	3.2	0.557
LH after LOD (IU/l)	12.3	3.0	9.8	1.3	0.061
LH/FSH before LOD	3.7	1.5	2.7	1.2	0.158
LH/FSH after LOD	3.8	1.7	3.4	2.2	0.722
Testosterone before LOD (nmol/l)	3.5	1.1	3.3	0.7	0.620
Testosterone after LOD (nmol/l)	2.4	0.8	2.6	0.3	0.341

Data are mean and standard deviation (SD).
*Unpaired t test.

As regard occurrence of pregnancy in patients with ovulation there were 8 cases (26% of the study group) showed clinical pregnancy as evidenced by positive quantitative B-hCG and a gestational sac by ultrasound examination.

In **table 7**, there was only a statistical significant difference as regard AMH After LOD between Patients who got pregnant and Patients without (*P.value* 0.040).

Table 8: receiver-operating characteristic (ROC) curve analysis for prediction of ovulation or clinical pregnancy

	Outcome	Ovulation		Clinical pregnancy
	Predictor	BMI before LOD	AMH after LOD	AMH after LOD
ROC curve parameter	AUC	0.795	0.866	0.794
	SE	0.109	0.109	0.113
	95% CI	0.576 to 0.933	0.660 to 0.971	0.576 to 0.932
	z statistic	2.692	3.366	2.610
	p-value*	**0.007**	**0.001**	**0.009**
	Youden index J	0.482	0.714	0.598
	Cut-off criterion	≤26.72 kg/m^2	≤7.97 ng/ml	≤5.86 ng/ml

	Sensitivity	62.5%	100%	83.3%
	Specificity	85.7%	71.4%	76.5%

AUC, area under the ROC curve; SE, standard error; 95% CI, 95% confidence interval.
*DeLong method.

Table 8 showed the results of receiver-operating characteristic (ROC) curve analysis for prediction of ovulation or clinical pregnancy

BMI before LOD and AMH after LOD had good value for prediction of ovulation (AUC = 0.795 and 0.866, respectively). The best cut-offs were a BMI of ≤26.72 kg/m^2 (sensitivity = 62.5%, specificity = 85.7%) and an AMH level of ≤7.97 ng/ml (sensitivity = 100%, specificity = 71.4%).

AMH after LOD had good value for prediction of clinical pregnancy (AUC = 0.794). The best cut-off was an AMH level of ≤5.86 ng/ml (sensitivity = 83.3%, specificity = 76.5%).

Table 9: correlations among total ovarian volume, AMH, ovarian Doppler indices and other quantitative variables before LOD

Variable		Total ovarian volume	AMH	Average ovarian RI	Average ovarian PI
Sum ovarian volume	*Pearson r*	-	-0.217	0.133	-0.256
	p-value	-	0.320	0.546	0.239
AMH	*Pearson r*	-0.217	-	0.216	**0.497***
	p-value	0.320	-	0.323	**0.016**
Average ovarian RI	*Pearson r*	0.133	0.216	-	0.081
	p-value	0.546	0.323	-	0.714
Average ovarian PI	*Pearson r*	-0.256	**0.497***	0.081	-
	p-value	0.239	**0.016**	0.714	-
Age	*Pearson r*	0.196	-0.054	0.152	0.133
	p-value	0.369	0.806	0.490	0.545
Age at menarche	*Pearson r*	-0.058	0.040	-0.396	0.086
	p-value	0.794	0.856	0.061	0.695
BMI	*Pearson r*	0.178	**-0.449***	-0.028	-0.205
	p-value	0.417	**0.032**	0.900	0.348
FSH	*Pearson r*	-0.206	0.028	0.028	0.090
	p-value	0.346	0.899	0.900	0.683
LH	*Pearson r*	-0.153	0.311	-0.065	0.007
	p-value	0.486	0.148	0.769	0.976
LH/FSH	*Pearson r*	0.058	0.177	0.148	-0.101
	p-value	0.792	0.419	0.499	0.646
Testosterone	*Pearson r*	-0.211	-0.241	-0.261	-0.230
	p-value	0.334	0.268	0.228	0.292
AFC	*Pearson r*	-0.317	0.043	-0.149	-0.019
	p-value	0.140	0.847	0.498	0.932

*. Correlation is significant at the 0.05 level (2-tailed).

In Table 9, in the patients before LOD, There was moderate positive correlation between AMH and average ovarian PI (*Pearson r* **0.497** and *P.value* **0.016**). While, AMH showed moderate negative correlation with BMI (*Pearson r* -**0.449** and *P.value* **0.032**)

Table 10: correlations among total ovarian volume, AMH, ovarian Doppler indices and other quantitative variables after LOD

		Total ovarian volume	AMH	Average ovarian RI	Average ovarian PI
Sum ovarian volume	*Pearson r*	-	-0.019	-0.157	**-.451***
	p-value	-	0.932	0.473	**0.031**
AMH	*Pearson r*	-0.019	-	-0.091	-0.351
	p-value	0.932	-	0.681	0.101
Average ovarian RI	*Pearson r*	-0.157	-0.091	-	-0.047
	p-value	0.473	0.681	-	0.830
Average ovarian PI	*Pearson r*	**-0.451***	-0.351	-0.047	-
	p-value	**0.031**	0.101	0.830	-
Age	*Pearson r*	0.243	**0.489***	0.079	-0.194
	p-value	0.264	**0.018**	0.722	0.375
Age at menarche	*Pearson r*	-0.007	**0.581****	0.127	-0.050
	p-value	0.975	**0.004**	0.564	0.820
BMI	*Pearson r*	-0.012	0.006	-0.154	0.011
	p-value	0.958	0.978	0.483	0.962
FSH	*Pearson r*	-0.072	0.071	-0.351	0.271
	p-value	0.746	0.749	0.101	0.211
LH	*Pearson r*	0.233	**0.475***	-0.142	-0.270
	p-value	0.285	**0.022**	0.518	0.213
LH/FSH	*Pearson r*	0.135	-0.038	0.286	-0.054
	p-value	0.538	0.864	0.186	0.806
Testosterone	*Pearson r*	0.132	0.164	0.195	-0.349
	p-value	0.549	0.454	0.372	0.103
AFC	*Pearson r*	-0.140	-0.031	-0.135	-0.049
	p-value	0.525	0.889	0.540	0.823

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

In **table** 10 in the patients after LOD, there was moderate Negative Correlation between Total (Sum) ovarian volume and average ovarian PI (*Pearson r* -0.451 and *P.value* 0.031). While, AMH showed moderate positive correlation with the age at the time of the study (*Pearson r* 0.489 and *P.value* 0.018), age at Menarche (*Pearson r* 0.581 and *P.value* 0.004) and LH levels (*Pearson r* 0.457 and *P.value* 0.022).

DISCUSSION

In this study found that age, age of menarche, BMI and duration of infertility did not significantly affect the results of our study.In a study by **Amer *et al.*** [(11)], they showed that ovulation and pregnancy rates are significantly decreased in patients with increasing duration of infertility (> 3 years) and increasing BMI (> 35 kg / m2). As regard hormonal profile, the hormonal profile of PCOS group (AMH, LH levels, LH: FSH ratio and total testosterone) were elevated. There was a significant difference between PCOS group and control group as regard AMH (P. value <0.001), LH (P. value <0.001), LH/FSH ratio (P. value 0.003) and Testosterone (P. value <0.001). AMH and testosterone had excellent diagnostic value for PCOS (AUCs = 1.0 and 0.987, respectively). The best cut-offs were an AMH level of >3.97 ng/ml (sensitivity = 100%, specificity = 100%) and a testosterone level of >2.23 nmol/l (sensitivity = 91.3%, specificity = 100%). AMH has been shown to be two to three-folds higher in serum from women with PCOS than in women with normal ovaries [(12)].

In this study, there was a statistical significant difference as regard total Testosterone before and after LOD in the study group with mean values 3.4 +/- 1 and 2.5 +/- 0.7 , respectively (P.value = 0.003). There was no

statistical significant difference as regard AMH (6.2 +/- 1.5 before and 6.6 +/- 1.5 after LOD with P.value = 0.483). Also there was no significant difference before and after LOD as regard LH (mean values were 12.7+/- 3.2 and 11.6 +/- 2.8, respectively with P.value = 0.273), LH/FSH ratio (P.value = 0.702) and FSH levels (mean values were 4.4 +/- 2.4 before and 4.2 +/- 2.1 after LOD with P.value = 0.776).

In a study carried out by **Elmashed *et al.*** [13] LH decreased insignificantly from 11.7+1.3 before LOD to 10.8+ 1.8 after LOD. FSH decreased insignificantly from (4.2+ 1.3) before LOD to 4.1+1.4 after LOD. Total testosterone decreased significantly from 4.2+ 0.4 nmol/L before LOD to 2.6+0.6 nmol/L after LOD.

In a study carried out by **Samy *et al.*** [14] LH decreased significantly from 12.57±4.28 before LOD to 9.35±3.12 after LOD and total testosterone decreased significantly from 2.79±1.6) to 1.98±1.13. As regard FSH, it decreased insignificantly from 6.34±2.83 before LOD to 6.33±2.44 after LOD.

In a study carried out by **Onofriescu *et al.*** [15] within 6 weeks after LOD. In their study, LH decreased significantly from 5.62±0.33 before LOD to 4.47±0.3 after LOD and total testosterone decreased significantly from 0.73±0.16 to 0.66 ± 0.11. As regard FSH, it increased significantly from 3.95 + 0.21 before LOD to 4.64 ± 0.21 after LOD**.**

In this study, 30% of PCOS group fail to respond to LOD. It may be due to the amount of electric current which was not sufficient to produce an effect in those patients. Another study revealed that LOD increased the endogenous FSH and only a minimal amount of thermal energy was required. Also, unilateral ovarian drilling is sufficient to produce ovulation in the responders. Another possible explanation may be an inherent resistance of the ovary to the effects of drilling. Another cause may be hyperprolactaenaemia observed in some patients after LOD. It is important to monitor the patients for prolactin levels after LOD. The drawback with LOD is to quantify the dose of diathermy to a particular patient. It is difficult to decide the dose for a particular patient without knowing the dose response. There is a need to optimize the dose of thermal energy in LOD in response to ovarian size [8]. In our study, we did not determine the amount of thermal energy according to the ovarian volume or size but the amount of thermal energy was fixed in all patients regardless the ovarian size.In this study, there was significant difference between PCOS group and control group as regard AFC (mean values were 52 +/- 12 and 17 +/- 6, respectively with P. value <0.001), average ovarian volume (11.9 +/- 1.4 and 9.7 +/- 1.2, respectively with P. value <0.001) and total ovarian volume (23.8 +/- 2.8 and 19.4 +/- 2.3, respectively with P. value <0.001). There was also significant difference between PCOS group and control group as regard Doppler indices presented in average ovarian RI (0.79 +/- 0.05 and 0.87 +/- 0.05, respectively with P. value <0.001) and average ovarian PI (2.28 +/- 0.40 and 3.32 +/- 0.65 with P. value <0.001).

In our study, the results of receiver-operating characteristic (ROC) curve analysis for discrimination between PCOS patients and the controls using total ovarian volume, ovarian RI and ovarian PI showed that total (Sum) ovarian volume, average ovarian RI and average ovarian PI had good value for discrimination between PCOS patients and controls (AUCs = 0.889, 0.865 and 0.891, respectively). The best cut-offs were a total ovarian volume of >19.1 ml (sensitivity = 100%, specificity = 65%), an average ovarian RI of ≤0.86 (sensitivity = 100%, specificity = 60%) and an average ovarian PI of ≤2.93 (sensitivity = 95.7%, specificity = 80%).

In this study, there was a statistical significant as regard AFC before and after LOD in patients with PCOS (52 +/- 12 and 35 +/- 17 with P.value 0.001). Also statistical significant difference before and after LOD as regard Doppler Indices in the form of Average Ovarian RI (0.79 +/- 0.05 and 0.82 +/- 0.05, respectively with P. value 0.039) and Average Ovarian PI (2.28 +/- 0.40 and 3.01 +/- 0.49, respectively with P.value <0.001). But there was no statistical significant difference as regard Sum Ovarian Volume before and after LOD (23.8 +/- 2.8 and 25.7 +/- 0.35, respectively with P.value 0.053).

In a study carried out by **Parsanezhad *et al.*** [16] PI increased significantly from 0.98 + 0.36 before LOD to 1.78 + 0.72 after LOD (*P.value = 0.001*). As regard RI, it increased significantly from 0.55 + 0.16 before LOD to 0.71+ 0.19 after LOD (*P.value = 0.001*)**.**

In study of **Abou Sekkein *et al.*** [17], PI increased insignificantly from 0.85 + 0.11 before LOD to 0.9 + 0.14 after LOD. In study of **Safdarian *et al.*** [18], PI increased significantly from 2.01 ± 0.64 before LOD to 2.89 ± 0.57 after LOD. As regard RI, it increased significantly from 0.76 ± 0.11 before LOD to 0.84 ± 0.08 after LOD**.**

In study of **Dolz *et al.*** [19] they suggested that the etiology of high ovarian stromal blood flow in PCOS patients is the abnormal timing of LH-dependent prostaglandin release.

In this study, in the patients before LOD, there was moderate positive correlation between

AMH and average ovarian PI (Pearson r 0.497 and P.value 0.016). While, AMH showed moderate negative correlation with BMI (Pearson r -0.449 and P.value 0.032).

While, in the patients after LOD, there was moderate negative correlation between sum ovarian volume and average ovarian PI (*Pearson r* -0.451 and *P.value* 0.031). While, AMH showed moderate positive correlation with the age at the time of the study (*Pearson* ***r*** 0.489 and *P.value* 0.018), age at Menarche (Pearson r 0.581 and *P.value* 0.004) and LH levels (Pearson r 0.457 and *P.value* 0.022).

In a study by **Parsanezhad *et al.*** [16] they found significant negative correlations between LH and PI (r = 0.43, P = 0.001), testosterone and PI (r = 0.40, P = 0.003), testosterone and RI (r = 0.30, P = 0.043), LH/FSH ratio and PI (r = 0.53, P < 0.001) and RI (r = 0.43, P = 0.001). While, correlation was useful in discovering possible connections between variables, it did not prove or disprove any cause-and-effect (causal) relationships between them.

A very rapid response has been reported following LOD in several studies, with ovulation occurring within 2- 4 weeks and menses within 4-6 weeks in the responders. Restoration of regular ovulatory cycles occurs in about two thirds of cases [11].

In this study menses and ovulation occurred in 21 patients (70% of cases) during the follow up period (8 weeks) and 9 patients (30% of cases) did not ovulate during the same period and we found that there is a statistical significant difference as regard BMI before LOD between Patients with Ovulation and Patients without Ovulation (*P.value* 0.024); also there is a statistical significant difference as regard AMH After LOD between Patients with Ovulation and Patients without Ovulation (*P.value* 0.002). Consequently, BMI before LOD and AMH after LOD had good value for prediction of ovulation (AUC = 0.795 and 0.866, respectively). The best cut-offs were a BMI of ≤26.72 kg/m2 (sensitivity = 62.5%, specificity = 85.7%) and an AMH level of ≤7.97 ng/ml (sensitivity = 100%, specificity = 71.4%).

Parsanezhad *et al.* [16] showed that the ovulation rate was 73.1% and more than reported by **Abou Sekkein *et al.*** [17] (69.23%) and **Amer *et al.*** [11] (67%). The cause for this difference in ovulation rate may be due to different techniques of drilling (monopolar or bipolar type of diathermy, Laser or diathermy, duration of electric current application, different number, diameter and depth of punctures and different amount of thermal energy).

In our study, as regard occurrence of pregnancy in patients with ovulation there were 8 cases (26% of the study group) showed clinical pregnancy during 6 months of follow up after LOD and there was only a statistical significant difference as regard AMH After LOD between Patients who got pregnant and Patients without (*P.value* 0.040). AMH after LOD had good value for prediction of clinical pregnancy (AUC = 0.794). The best cut-off was an AMH level of ≤5.86 ng/ml (sensitivity = 83.3%, specificity = 76.5%).

In this study, we reported our findings regarding the effects of LOD on AMH, hormonal profile and ovarian stromal blood flow in anovulatory PCOS women with Clomiphene resistance. These results suggest that the measurement of AMH, LH, LH/FSH ratio, total testosterone, ovarian volume and ovarian stromal blood flow may be of value in discrimination of PCOS from potentially fertile women.The data in this study suggests that there were no significant differences as regard AMH, Hormonal profile except total Testosterone, ultrasound ovarian findings and ovarian stromal blood flow before and after LOD but there was significant differences as regard total Testosterone before and after LOD.Also, there was a good predictive value for AMH after LOD for ovulation and clinical pregnancy.Comparing LOD for PCOS patients with other surgical interventions like ovarian wedge resection which was done formerly, we found that other studies had confirmed the benefits of the procedure of wedge resection, with varying rates of success in resumption of ovulatory cycles and pregnancy rates. However, It was clear, that the procedure was often associated with the development of periadnexal adhesions obviating the beneficial effects of surgery [20], but with modified ovarian wedge resection with anti-adhesion techniques that progressed sufficiently to be able to feel confident that a surgical procedure such as modified ovarian wedge resection could be performed without any great risk of forming adhesions [20].

CONCLUSION

PCOS is a common problem in infertility practice. Its management requires at first orientation by its pathophysiology. To induce ovulation in infertile patients with PCOS, this requires lifestyle modification (weight loss, exercise and diet control) in addition to medication which induces ovulation such as clomiphene citrate and gonadotrophins, or surgical induction of ovulation by laparoscopic ovarian drilling.

RECOMMENDATIONS

Laparoscopic ovarian surgery should be offered as a second line for all anovulatory women with PCOS who fail to respond to CC and need a laparoscopic assessment of their pelvis or who live too far away from the hospital not able to attend for the intensive monitoring required of gonadotropin therapy.

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