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Evaluation of Ultrasonographic and Anti-Müllerian Hormone (AMH) Changes as Predictors for Ovarian Reserve after Laparoscopic Ovarian Drilling Versus Conservative Treatment for Women with Polycystic Ovarian Syndrome

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ABSTRACT

Background: Until recently, there was no international consensus either on the definition of polycystic ovarian syndrome (PCOS) or on what constitutes a polycystic ovary. At a recent consensus of The European Society of Human Reproductive and Embryology/American Society of Reproductive Medicine (ESHRE/ASRM), a refined definition of the PCOS was agreed: namely two out of the following three criteria; Oligo- and/or anovulation, Hyperandrogenism (clinical and/or biochemical) and Ultrasonographic features of PCOS.

Aim of the Work: evaluation of ovarian volume, antral follicles count and anti mullerian hormones as predictors of ovarian reserve after conservative treatment versus laparoscopic ovarian drilling in women with polycystic ovarian syndrome.

Patients and Methods: This prospective controlled study was conducted on 20 women attending Outpatient Clinics of Al Hussein University Hospital & Aswan University Hospital for infertility treatment. It was conducted between January 2016 and February 2018.

Results: No significant difference was found between clomiphene citrate (CC) and laparoscopic ovarian diathermy (LOD) groups regarding to AFC and summed ovarian volume in follow up periods, (P= 0.645,P=0.401//P=0.238, P=0.301) respectively. There was a highly significant difference between CC, LOD and control groups regarding to AMH ($P < 0.001$) after 6 months of treatment. The study revealed that there was no statistically significant difference between groups according to clinical & reproductive outcomes.

Conclusion: The relative contribution of each individual measure of the ovarian reserve is clearer and most authors agree that antral follicle counts and serum anti-müllerian hormone levels had the most discriminative. Antral follicle counts are easy to perform and cheap in comparison as all units had access to ultrasound facilities. Follicle counts, as a quantitative measure of the ovarian reserve, are also subject to 'assay' variation due to intra- and inter-observer differences and require additional time and manpower to perform.

Keywords: ultrasonography, anti-müllerian hormone, ovarian reserve, laparoscopic ovarian drilling, conservative tremens, PCOS

INTRODUCTION

According to the revised 2004 consensus on diagnostic criteria of polycystic ovarian syndrome (PCOS) of Rotterdam European Society of Human Reproduction and Embryology/ American society of reproductive medicine (ESHRE/ASRM) sponsored PCOS 2003 consensus workshop group, the PCOS was defined as two out of the following three criteria (after exclusion of specific underlying diseases of the adrenal or pituitary glands): Oligo- or Anovulation, Hyperandrogenism, and the presence of 12 or more follicles per each ovary ranging from 2 to 9 mm in diameter or ovarian volume of more than 10 cm3 [1].

Laparoscopic ovarian diathermy (LOD) is a treatment method for PCOS, which has replaced a more invasive and damaging technique of ovarian wedge resection. The mechanism of action of LOD is still uncertain. A hypothesis suggests that a minimal injury to an unresponsive ovary either restores the ovulatory cycle or increases responsiveness to gonadotropins stimulation.

The term "ovarian reserve" (OR) refers to the size of the non-growing or resting primordial follicle population, which presumably determines the numbers of growing follicles and the quality or reproductive potential of their oocytes [2].

The tests of ovarian reserve are of two types either stimulatory tests or non-stimulatory tests. The stimulatory tests are also termed "the ovarian challenge tests" or dynamic ovarian reserve tests. They may be performed by administrating clomiphene citrate or a GnRH agonist. The non-stimulatory tests include measuring basal follicular stimulating hormone (FSH) level, Antral follicles count (AFC), ovarian volume assessment, Inhibin-B level, and Anti-Müllerian Hormon(AMH) level [3].

The basal FSH level in the serum is the most commonly used test, in routine practice, to assess the ovarian function and its disorders;

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perimenopause, menopause and premature ovarian failure. It is based on evidence that small increase in basal serum FSH level correlates with decreased fertility rates seen among women in their late thirties. That is to say, that elevated FSH level indicates diminished ovarian reserve (DOR).

The antral follicle is a stage of follicular growth when the follicle acquires a cavity or an antrum containing steroid hormones so it can be visualized by ultrasound as hypoechoic or black part due to its fluid content. However, neither the earlier stages of follicular growth nor the resting primordial follicles can be visualized by the ultrasound. Presumably, the visible AFC on ultrasound is indicative of the relative number of microscopic primordial follicles remaining in the ovary because each primordial follicle can potentially develop in the future to antral follicle.

The AFC assessment by pelvic ultrasound has been reported as the single best indicator of poor ovarian response to stimulation for IVF [4].

The ovarian volume is increased in PCOS because of the multiple arrested ovarian follicles. That is why the volume is reduced after drainage of these follicles by LOD. A reduced ovarian volume does not necessarily mean reduced AFC [5].

As well as around the world polycystic ovarian syndrome is thought to be one of the leading causes of female infertility and represents an actual problem in gynecology. It affects 4% to 12% of women of reproductive age and is the major factor of anovulatory infertility [6]. Its prevalence particularly is increased in adolescents [7]. This population deserves attention considering the future fecundity and long term reproductive results [8]. Because women with PCOS have high numbers of antral follicles, high AMH levels are often seen as well. Besides being used as a potential diagnostic marker for PCOS, AMH is used as an indicator of ovarian reserve as a predictor of ovarian response to stimulation during In Vitro Fertilization (IVF), that is especially important in women of late reproductive age [9,10].

Aim of the Work

This study aims to evaluate ovarian volume, antral follicles count and anti mullerian hormones as predictors of ovarian reserve after conservative treatment versus laparoscopic ovarian drilling in women with polycystic ovarian syndrome.

Patients and Methods

Patients of our prospective controlled study were recruited from women attending to the Outpatient Clinics of Al Hussein University Hospital & Aswan University Hospital for infertility treatment. It was conducted between January 2016 and February 2018.

The study included 40 (n = 40) primary anovulatory women with PCOS, who were divided into LOD group (n = 20), who were CC resistant PCOS (who had failed to ovulate before and after maximum CC dose for at least 3 cycles). Another group receiving incremental doses (50–150 mg) of CC (n = 20) and a third group including 20 healthy age-matched women with a regular menstrual cycle and normal ovaries (confirmed with ultrasound examination) as the control group.

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 each of the participants before being included in the study.

The patients were selected according to the following:

1) Inclusion criteria:

Patients were:

1. Less than 35 years old in age.
2. Complaining of primary infertility.
3. Exhibiting revised Rotterdam criteria of PCOS.
4. Free of ovulation induction drugs for at least 3 months before the procedure (for the LOD group).
5. Have body mass index (BMI) of less than 30.
6. Indicated for LOD:
   a. Anovulatory PCOS with clomiphene citrate resistance.
   b. Persistent hypersecretion of LH.
7. No past history of other ovarian pathology.
8. No past history of any previous ovarian surgeries.

2) Exclusion Criteria

1. More than 35 years old age.
2. History of medical disorders, specially pituitary or hypothalamic disorders.
3. History of pelvic surgical open or laparoscopic operation especially ovarian operations.
4. History of ovarian diseases; tumors, pathological cysts, endometrosis, or tubo-ovarian abscess.
5. History of ovulation induction drugs during the last three months before the procedure (for the LOD group).

3) Methods:

a) History taking:

Complete history taking with special emphasis on age, menstrual pattern, marital history, sexual history and previous abdominal operations.

b) examination:

i) General examination:

Commenting on the vital signs (blood pressure, pulse and temperature), the general appearance (pallor or jaundice), head and neck (thyroid, lymph nodes, congested neck veins and septic foci), chest (breasts, lungs and heart) and

upper and lower limbs (varicose veins, edema and clubbing).

ii) Abdominal examination:

For the presence or absence of organomegaly, pelviabdominal masses, skin manifestations and hair distribution.

iii) Local pelvic examination:

For the site, size, regularity, mobility and descend of the uterus and the presence of adnexal tenderness or masses.

c) Routine investigations:

Including complete blood count (with special emphasis on hemoglobin percent and hematocrit value), bleeding time, prothrombin time and activity, urine analysis, blood urea and creatinine, liver function tests and glucose tolerance test.

d) Study specific Investigations:

i) Imaging studies:

Two dimensional (2D) transvaginal ultrasound was performed at our Inpatient's Ultrasound Unit. The Transvaginal ultrasound examination (TVS) was done using a 7.5-mHz transducer (TOSHIBA SSA 270 AUS machine, Toshiba Co., Tokyo, Japan) for all women of all three-study groups. Transvaginal ultrasound examination was done to confirm the presence of the diagnostic ultrasound criteria of PCOS, to evaluate endometrial thickness, ovarian volume, to check the antral follicle count and to exclude other pelvic pathology.

Procedure for measuring the AFC:

Antral follicles were defined as all echo lucent rounded structures measuring 2–10 mm seen within the ovarian substance.

The volume of both ovaries was then summed and divided by 2 to find the average volume of both ovaries that was the statistic variable of ovarian volume in the study. Ovarian volume = length × width × thickness × 0.523. The procedure was repeated on the contra lateral ovary and the sum of volumes of both ovaries was calculated giving the total summed ovarian volume (SOV).

Laboratory investigations:

Blood samples were collected before and one week after LOD to measure plasma concentrations of AMH, LH, FSH, and other hormones. Further blood samples were collected 3 and 6 months after LOD for the hormonal assays. Similarly, in women receiving clomiphene citrate, hormonal assays were measured before treatment, on cycle Day 2 of the following menstrual cycle, and at 3- and 6-month follow-up.

Ovulation induction by CC and LOD

Group 1 (CC group): clomiphene citrate was given in 150 mg dose per day for up to six cycles starting in the second day and for 5 days of a menstrual cycle or after a progestogen withdrawal bleeding.

Group 2 (LOD group): Laparoscopic ovarian electrocautery was done just after the end of the menstruation. This group was clomiphene citrate resistant cases.

Group 3 (control group): healthy age-matched women with a regular menstrual cycle and normal ovaries (confirmed with ultrasound examination).

Detailed surgical procedure of laparoscopic electrocautery:

The same experienced operator performed the laparoscopic procedures during the early post-menstrual phase (spontaneous or withdrawn).

All punctures were done on antimesentric border to protect against damage to the ovarian blood supply.

Clinical and reproductive outcome:

All Patients were followed up until they successfully conceived or for up to 6 months period. The main outcome measures included menstrual pattern, ovulation rate, pregnancy rate and the ovarian reserve. Evaluation of those parameters was done at the beginning of the study, one month after treatment and at 3 and 6 months follow up periods.

Transvaginal ultrasound examination.

(1) AMH in the third cycle day.

(2) antral follicle count (AFC) by TVS.

(3) summed ovarian volume (SOV) by TVS.

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- A one-way analysis of variance (ANOVA) when comparing between more than two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:
  - P-value < 0.05 was considered significant.
  - P-value < 0.001 was considered as highly significant.
  - P-value > 0.05 was considered insignificant.

RESULTS

Table (1): Comparison between groups according to demographic data and general examination

Demographic data and general examination		Group I: CC (N=20)	Group II: LOD (N=20)	Group III: Control (N=20)	F/x2#	p-value
Age (years)	Mean ± SD	27.00 ± 3.73	26.00 ± 3.57	26.80 ± 3.49	0.433	0.651
	Range	22-35	20-31	20-32		
Pattern of menstruation	Regular cycle	0 (0.0%)	0 (0.0%)	20 (100.0%)	60.000#	<0.001**
	Oligomenorrhea	2 (10.0%)	2 (10.0%)	0 (0.0%)		
	Amenorrhea	18 (90.0%)	18 (90.0%)	0 (0.0%)		
BMI [wt/(ht)2]	Mean ± SD	26.40 ± 2.09 [a]	27.95 ± 2.35[a]	24.25 ± 1.74 [b]	3.957	0.031*
	Range	24-32	24-32	20-27		
Waist/ hip ratio	Mean ± SD	0.76 ± 0.18 [a]	0.82 ± 0.02 [a]	0.70 ± 0.07 [b]	3.18	0.019*
	Range	60-0.83	0.79-0.89	0.58-0.8		
ACNE		8 (40%)	9 (45%)	2 (10%)	6.624#	0.036*
Hirsutism		11 (55.0%)	11 (55.0%)	3(15.0%)	12.114#	<0.001**
Acanthosis nigricans		0 (0.0%)	0 (0.0%)	0 (0.0%)	0.000#	1

This table showed No statistically significant difference between all groups according to baseline characters as (age and acanthosis nigricans). However, there was a highly significant difference between women with anovulatory PCOS (CC and LOD groups) compared to 20 age-matched healthy women (control group) with a regular menstrual cycle as regards pattern of menstruation and hirsutism, (p-value < 0.001). Also, there was statistically significant difference between women with anovulatory PCOS (CC and LOD groups) compared to the control group (age-matched healthy women with a regular menstrual cycle) in regard to BMI, Waist/hip ratio and acne (P-value = 0.031, = 0.019 and = 0.036 respectively).

Table (2): Comparison between groups according to ultrasound findings

	Ultrasound Findings	Group I: CC (N=20)	Group II: LOD (N=20)	Group III: Control (N=20)	F	p-value
Before treatment	**AFC**					
	Mean ± SD	15.35 ± 2.74[a]	15.50 ± 2.59[a]	5.74 ± 1.15[b]	115.47	<0.001**
	Range	20-Dec	20-Dec	8-Apr		
	Summed ovarian volume					
	Mean ± SD	13.29 ± 1.83[a]	13.27 ± 1.71[a]	6.27 ± 1.40[b]	114.876	<0.001**
	Range	10.5-16.2	10.5-16.2	4.2-9.3		
3 months after treatment	**AFC**					
	Mean±SD	13.85 ± 2.37[a]	13.50 ± 2.40[a]	5.74 ± 1.15[b]	12.408	0.007*
	Range	18-Nov	18-Oct	8-Apr		
	Summed ovarian volume					
	Mean ± SD	9.92 ± 1.66[a]	10.38 ± 1.76[a]	6.27 ± 1.40[b]	3.717	0.011*
	Range	6-11.3	14-Jun	4.2-9.3		
6 months after treatment	**AFC**					
	Mean ± SD	12.05 ± 2.01[a]	11.35 ± 1.66[b]	5.74 ± 1.15[c]	10.368	0.004*
	Range	16-Oct	16-Sep	8-Apr		
	Summed ovarian volume					
	Mean ± SD	8.23 ± 1.77	8.78 ± 1.54	6.27 ± 1.40	2.279	0.229
	Range	5.9-11.2	5.9-11.2	4.2-9.3		
AMH	**Before treatment**					
	Mean ± SD	5.36 ± 0.96[a]	5.30 ± 0.97[a]	2.05 ± 0.40[b]	106.062	<0.001**
	Range	3.5-6.72	3.5-6.75	1.5-2.86		
	3 month after treatment					
	Mean ± SD	4.03 ± 0.68[a]	3.11 ± 0.98[b]	2.05 ± 0.40[c]	12.821	<0.001**
	Range	2.9-5.2	3.4-6.7	1.5-2.86		
	6 months after treatment					
	Mean ± SD	4.12 ± 0.73[a]	3.02 ± 0.98[b]	2.05 ± 0.40[c]	11.274	<0.001**
	Range	2.9-5.5	3.4-6.7	1.5-2.86		

Table 2 showed highly statistically significant difference between CC and LOD groups compared to the control group concerning baseline AFC and summed ovarian volume ($p < 0.001$). However, no statistically significant difference was found between CC and LOD groups.

There was also no significant difference between CC and LOD groups regarding the AFC and summed ovarian volume in follow up periods (P = 0.645, P = 0.401, P = 0.238 and P = 0.301 respectively).

Regarding to AMH:

- Baseline AMH levels were significantly higher in the CC and LOD groups than in the control group ($p < 0.0001$), but without a statistically significant difference found between CC and LOD groups ($p = 0.282$).
- There was highly significant difference between CC, LOD and control groups regarding AMH ($P < 0.001$) after 3 months of treatment.
- There was highly significant difference between CC, LOD and control groups in regard to AMH ($P < 0.001$) after 6 months of treatment.

Table (3): Comparison between groups according to laboratory investigations (before treatment)

Laboratory investigations (Before treatment)	Group I: CC (N=20)	Group II: LOD (N=20)	Group III: Control (N=20)	F	p-value
FSH					
Mean ± SD	6.23 ± 1.15 [a]	6.13 ± 1.26 [a]	4.38 ± 1.22 [b]	14.769	<0.001**
Range	4.1-8.6	4.1-8.6	2.7-6.46		
LH					
Mean ± SD	13.02 ± 2.42 [a]	12.65 ± 2.68 [a]	3.96 ± 1.21 [b]	109.015	<0.001**
Range	9.5-19.1	8.2-19.1	2.6-6.41		
LH/ FSH ratio					
Mean ± SD	2.10 ± 0.13 [a]	2.08 ± 0.10 [a]	0.90 ± 0.12 [b]	668.188	<0.001**
Range	1.98-2.3	2-2.3	0.57-1.15		
E2					
Mean ± SD	44.34 ± 14.53	45.70 ± 11.54	45.45 ± 11.52	0.066	0.936
Range	28-78	25-64	29-63		
Prolactin					
Mean ± SD	10.50 ± 4.05 [a]	9.05 ± 2.18 [a]	7.05 ± 1.30 [b]	7.875	<0.001**
Range	5.7-23.7	5.7-14	4.68-9.2		

This table showed statistically significant difference between groups concerning laboratory investigations before treatment. Besides, the table showed that baseline FSH, LH, and the LH : FSH ratio were significantly higher in CC and LOD groups as compared to the control group ($p < 0.001$) but no statistically significant difference was found between CC and LOD groups ($p = 0.380$, $p = 0.194$ and $p = 0.501$) respectively.

In addition, no statistically significant differences were found between all groups regarding baseline E2 levels (P = 0.936).

Baseline AMH levels were significantly higher in the CC and LOD groups than in the control group ($p < 0.0001$), but without a statistically significant difference found between CC and LOD groups (p value = 0.282).

Comparison between Group I: LOD & Group II: CC in regard to:
FSH (p = 0.380), LH (p = 0.194),
LH/ FSH ratio (p = 0.501) and **E2 (p = 0.484)**
Prolactin (p = 0.246)

Table (4): Comparison between groups concerning clinical & reproductive outcomes

Clinical & reproductive outcomes	Group I: CC (N=20)	Group II: LOD (N=20)	x2	p-value
Before treatment				
Ovulation rate	0 (0.0%)	0 (0.0%)	--	--
Pregnancy rate	0 (0.0%)	0 (0.0%)	--	--
Menstrual Pattern (regular)	0 (0.0%)	0 (0.0%)	--	--
3 months after treament				
Ovulation rate	10 (50%)	9 (45%)	0.004	0.945
Pregnancy rate	2 (10%)	2 (10%)	0.000	1.000
Menstrual Pattern (regular)	10 (50%)	14 (70%)	0.937	0.333
6 months after treament				
Ovulation rate	13 (65%)	12 (60%)	0.004	0.945
Pregnancy rate	7 (35%)	6 (30%)	0.004	0.945
Menstrual Pattern (regular)	13 (65%)	15 (75%)	0.119	0.730

This table showed no statistically significant difference between groups in regard to clinical & reproductive outcomes.

Table (5): The extent of the difference over the periods through laboratory investigations in group I

Laboratory investigations	Group II: CC (N=20)				ANOVA	
	Before treatment	1 month after treatment	3 months after treament	6months after treament	F	p-value
FSH	6.23 ± 1.15	6.84 ± 1.16	6.44 ± 1.17	6.43 ± 1.11	0.181	0.290
LH	13.02 ± 2.42	11.92 ± 2.30	11.94 ± 2.33	11.92 ± 2.30	1.571	0.064
LH/ FSH ratio	2.10 ± 0.13	1.78 ± 0.12	2.13 ± 1.36	1.88 ± 0.12	1.89	0.113
E2	44.34 ± 14.53	46.90 ± 14.50	47.35 ± 14.58	47.35 ± 14.58	1.346	0.081
AMH	5.36 ± 0.96	4.07 ± 0.71	4.03 ± 0.68	4.12 ± 0.73	1.195	0.075

This table showed that:

- There were no significant changes in the FSH throughout the follow-up periods after CC treatment. In the CC group, FSH levels slightly increased a week and 3-months after treatment, and then gradually returned to baseline values at 6-months but without significant changes.
- LH and the LH : FSH ratio did not show significant changes during the follow up periods. In the CC group, estradiol levels (E2) increased slightly during the first week then increased at 3- and 6-months of follow-up but without statistical significant changes.
- Following up CC group, there were no significant changes in the AMH levels between the baseline and at 3-month or 6-month periods after treatment.

Table (6): The extent of the difference over the periods through laboratory investigations in the group II

Laboratory investigations	Group II: LOD (N=20)				ANOVA	
	Before treatment	1 month after treatment	3 months after treament	6months after treament	F	p-value
FSH	6.13 ± 1.26	6.04 ± 1.42	6.16 ± 1.26	6.12 ± 1.27	1.062	0.482
LH	12.65 ± 2.68	10.65 ± 2.68	9.66 ± 2.67	9.64 ± 2.67	4.869	<0.001**
LH/ FSH ratio	2.08 ± 0.10	1.45 ± 0.10	1.36 ± 0.10	1.27 ± 0.10	6.418	<0.001**
E2	45.70 ± 11.54	45.85 ± 11.27	45.40 ± 11.10	45.95 ± 11.43	0.196	0.291
AMH	5.30 ± 0.97	4.25 ± 0.96	3.11 ± 0.98	3.02 ± 0.98	7.641	<0.001**

This table showed that:

- There was no significant changes in the FSH throughout the follow-up periods after LOD. FSH decreased shortly after LOD, then gradually increased returning to baseline values but without significant changes.
- Regarding the LH and the LH : FSH ratio there was statistically highly significant decrease a month after LOD and remained low at 3- and 6-month follow-up periods ($P < 0.001$).
- In the LOD group, estradiol levels (E2) increased slightly during the first month after LOD, then remained increased at follow-up periods but without statistical significance (p value = 0.291).
- Following up LOD, AMH level significantly decreased after one month and remained low at 3- and 6-month follow-up periods (p value < 0.001).

DISCUSSION

In the present study, the age ranged from 22-35 years old with a mean value 27.00 ± 3.73 years old for the CC group and ranged from 20-31 years old with a mean value of 26.00 ± 3.57 years old for the LOD group. The distribution of age approaches normal distribution without significant skewness or outliers that constitute a homogenous group of patients' ages. We excluded from the study patients with more than 35 years old age because of age-related decline in ovarian reserve

There was no significant difference between the age groups in our study and other studies. **Roy *et al.*** [11] reported a mean age of 28.42 ± 3.65 years old. In **Mansour *et al*.** [12] study, the mean age of patients was 26.54 ± 4.72 years old. This also agreed with **Safia et al.** [13] where the mean age of patients was 25.3 ± 3.4 years old and **Cynthia *et al.*** [14] where the mean age of patients was 29.6 ± 4.7 years old. However, in **Kandil *et al.*** [15], they selected an older group of ages where the mean age of the patients was 34.1 ± 4 years old.

The BMI of women in the study ranged from 24 – 29 kg/m^2 with a mean value of 26.40 ± 2.09 kg/m^2 for the CC group and ranged from 24-29 kg/m2 with a mean value 27.95 ± 2.35 kg/m2 for the LOD group. The BMI distribution approaches normal distribution without skewness or outliers that constitute a homogenous group of patients' BMI. The BMI in the study was falling in the category of normal body weight and overweight. Cases with BMI of 30 or more were also excluded because of low incidence of ovulation in obese group, and weight loss is recommended prior to treatment and LOD.

There was no significant difference between patients' BMI in this study. Our results are consistent with **Roy *et al.*** [11] (mean BMI 24.12 ± 4.87 kg/m^2), **Mansour *et al.*** [12] (BMI mean of 25.54 ± 2.31 kg/m^2), **Kandil *et al.*** [15] (mean BMI was 28 ± 2.1 kg/m^2), **Safia *et al.*** [13] where the mean BMI was 26.96 ± 3.05 kg/m^2 and **Cynthia *et al.*** [16] who reported a mean BMI of 28.3 ± 3.9 kg/m^2.

About 90.0% of patients had irregular menstrual cycle in the form of oligomenorrhoea while the other 10.0% had amenorrhea for both groups. This was because of chronic anovulation and hyper-estrogenic state of PCOS. No cases with normal pattern menstrual cycle were present in the study. In addition, about 55.0% of patients had hirsutism for both groups and 40.0% and 45.0% of the patients of CC group and LOD group respectively had acne. This could be attributed to increased androgen levels in PCOS.

There were little variations in percentages of menstrual irregularity and signs of hyperandrogenism with other studies. **Amer *et al.*** [17] reported that about 70% of cases suffered from soligomenorrhea while 33% of cases had acne and hirsutism. In addition, **Cynthia *et al.*** [16] showed that about 56% of cases had amenorrhea, 44% had oligomenorrhea, 46% had acne and 60% had hirsutism. In **Safia *et al.*** [13] study, about 63.3% of cases had oligomenorrhea, 30% had amenorrhea, 75.5% had hirsutism and 32.7% had acne.

In the current study, the PCOS women in LOD group, 15/20 (75%) had regular cycles while the ovulation rate was 12/20 (60%) and the pregnancy rate was 6/20 (30%) in the 6-month period after LOD. These results are in agreement with **Poujade *et al.*** [18], **Sowers *et al.*** [19], **Maheshwari *et al.*** [20], **Nardo *et al.*** [21] and **Kwee *et al.*** [22].

Parsanezhad *et al.* [23] and Farquhar et al. [24]. described the success and utility of this procedure, with ovulation rates ranging from 64% to 92% and pregnancy rates from 41% to 80%.

In the present study, 14/20 (70%) women with PCOS were still resistant to LOD and did not conceive despite high ovulation rate being observed. A possible explanation is that the amount of ovarian tissue destroyed during LOD was not enough to induce favorable changes on reproductive parameters in some patients such as intra-ovarian AMH levels.

As regards to the AFC in LOD group, Before treatment AFC ranged from 12-20 with a mean value of 15.50 ± 2.59 follicles. This high AFC caused by the chronic anovulation and presence of multiple arrested follicles in PCOS. The postoperative third cycle AFC ranged from 10-18 with a mean value of 13.50 ± 2.40 follicles. There

was high significant decrease in the postoperative third and sixth cycles AFC as compared to preoperative AFC. This could be attributed to the drainage effect of LOD on the multiple arrested follicles. On the other hand, there was no significant difference between the postoperative third cycle and postoperative sixth cycle AFC. The AFC remained within the normal range, so we could infer that LOD normalized the AFC without causing diminished ovarian reserve DOR.

In comparison with other studies, **Kandil and Selim** [15] reported that the preoperative AFC mean was 16.5 ± 1.3 follicles, while at 3 months postoperatively AFC had a mean of 14.9 ± 2.1 follicles. There was a significant difference between the preoperative and postoperative AFC. In addition, **Amer *et al.*** [17] studied the long-term ultrasonic changes of LOD of PCOS patients. They found a decrease in ultrasonic features characterizing PCOS (regarding ovarian volume and AFC), while the values remained within the high normal range. That is agreed with our results. In a study by **Sawaek *et al.*** [25], comparing AFC between PCOS patients who underwent LOD and a control group. They reported a significant decrease in AFC in the LOD group in comparison with the control group however, the AFC stayed within normal range. In addition, **Murat *et al.*** [26] also reported a significant decrease in AFC after LOD, however, the AFC stayed in the high normal range. These results also agreed to our results.

As regards, the summed ovarian volume, the preoperative summed ovarian volume in our study ranged from 10.5-16.2 with a mean of 13.27 ± 1.71 cm^3. This large summed ovarian volume was attributed to the presence of multiple arrested follicles. The postoperative third cycle summed ovarian volume ranged from 6–14 with a mean of 10.38 ± 1.76 cm^3 while the postoperative sixth cycle ovarian volume ranged from 5.9-11.2 with a mean of 8.78 ± 1.54 cm^3. There was a significant decrease in the postoperative third cycle and postoperative sixth cycle summed ovarian volume as compared to the preoperative summed ovarian volume. This could by attributed also to the drainage effect of LOD on the multiple arrested follicles. On the other hand, there was no significant difference between the postoperative third cycle and postoperative sixth cycle summed ovarian volume. The summed ovarian volume remained within the normal ranges, so we could infer that LOD normalized the ovarian volume without causing diminished ovarian reserve DOR.

In comparison with the others, **Talundi *et al.*** [27] reported that the mean preoperative summed ovarian volume was 12.2 ± 1.8 cm^3 while the mean postoperative summed ovarian volume after 3 weeks of LOD was 6.9±1.3 cm^3. There was a significant decrease in summed ovarian volume after LOD. These findings are in consistence with our results. In **Cynthia *et al.*** [16], the mean preoperative summed ovarian volume was 11.3 ± 5.7 cm^3 while the mean summed ovarian volume at 6 months postoperatively was 4.9 ± 5.2 mm^3. There was a significant decrease in summed ovarian volume after LOD. However, summed ovarian volume remained in the normal range. In addition, **Kandil and selim** [15] reported a mean preoperative summed ovarian volume of 11.5 ± 1.0 cm^3 while the mean summed ovarian volume after 3 months was 10.3 ± 1.1 mm^3. There was a significant reduction in ovarian volume after LOD however, the values remained in the normal range. These findings also agreed with our results.

Our study confirmed that there was no significant changes in the serum concentration of FSH throughout the follow-up periods after LOD. FSH concentrations increased shortly after LOD, and then gradually returned to baseline values but without significant changes. The present study agreed with **Amer *et al.*** [28] where the mean FSH level preoperatively was 6.13 ± 1.26 mIU/ml and the mean postoperative FSH level after one month was 6.04 ± 1.42mIU/ml. There was no statistical difference between the preoperative and postoperative basal FSH levels. Our results were also in agreement with **Safia *et al.*** [13].

Estradiol levels (E2) increased slightly during the first week after LOD then increased at 3- and 6-months of follow-up but without statistical significant difference in E2 levels between pre and post LOD. These findings are in agreement with many previous studies [28,29,30].

Our study concluded that the baseline AMH levels did not show statistically significant difference between LOD and CC groups. There was significant high levels of plasma AMH in women with anovulatory PCOS compared to healthy controls. These results are in agreement with the study of **Seyam *et al.*** [31]. Other previous studies showed that women with PCOS had 2–3 times increased level of serum AMH concentration which was related to increment in the number of small follicles. [14,32] .

There were no significant changes in the FSH throughout the follow-up periods after LOD or CC treatment. FSH increased shortly after LOD, and then gradually returned to baseline values but without significant changes. In the CC group, FSH levels slightly increased a month and 3-months after treatment, and then gradually returned to baseline values at 6-months but without significant changes. This result agreed with **Seyam *et al.*** [31].

As regards LH and the LH : FSH ratio, our study agreed with the study done by **Seyam *et al.*** [31] as there was significant decrease a month after LOD and remained low at 3- and 6-month follow-up periods. However, in the CC group, LH and the LH : FSH ratio did not show significant changes during the same time periods.

Following LOD, AMH level significantly decreased after one month and remained low at 3- and 6-month follow-up. In the CC group, there were no significant changes in the AMH levels between the baseline and at 3-month or 6-month periods after treatment. This results agreed with study done by **Seyam *et al.*** [31]**.**

CONCLUSION

- There was no difference between CC group and LOD group in clinical and reproductive outcomes as regards ovulation rate, pregnancy rate and menstrual pattern.
- The relative contribution of each individual measure of the ovarian reserve was clearer and most authors agreed that antral follicle counts and serum Anti-Müllerian Hormone levels have the most discriminative. Antral follicle counts are easy to perform and cheap in comparison as all units have access to ultrasound facilities. Follicle counts, as a quantitative measure of the ovarian reserve, are also subject to 'assay' variation due to intra- and inter-observer differences and require additional time and manpower to perform.
- LOD had appeared after the study not to be associated with an increased risk of diminished ovarian reserve. Most of the changes in the ovarian reserve markers raised with the current work after LOD that could be interpreted to be due to normalization of ovarian function in the enrolled PCO women rather than the reduction of the ovarian reserve.

RECOMMENDATIONS

1- Counselling and Lifestyle modifications (Obesity negatively affects the efficacy of any infertility treatment).

2-- 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.

3- The AMH can be used as reliable markers of the ovarian reserve and measuring them for women with anovulatory PCOS undergoing LOD may provide a useful tool in evaluating the outcome of LOD.

Advantages and pitfalls

Advantages

- Prospective cohort study.
- Multicentric study.
- The study revealed that no significant difference in both CC group and LOD group in clinical and reproductive outcomes in regard to ovulation rate, pregnancy rate and menstrual pattern.

Pitfalls

- Longitudinal follow up for assessment of ovarian reserve for women with anovulatory PCOS was deficient.
- The lack of long-term evidence and the risks of surgery.
- Second-line intervention for CC resistant cases: laparoscopic ovarian surgery (LOS) or Gn stimulation but our study restricted to LOS only

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