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Studying the Effect of Laparoscopic Ovarian Drilling on Ovarian Reserve via Measurement of Anti-Mullerian Hormone in Polycystic Ovarian Syndrome Patients

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is the most common cause of anovulation and it also causes other metabolic and endocrinal disorders. Lines of management of PCOS include several medical options in addition to laparoscopic ovarian diathermy (LOD). However, the effect of LOD on ovarian reserve has always been a concern. Advocates to LOD claimed that the decrease in ovarian reserve following LOD is merit not a drawback. **Study Design:** A case series study aimed at investigating the effect of LOD on Anti-Mullerian hormone (AMH) and trying to find the relation between AMH levels and success of LOD. **Patients and Methods:** The study was carried out on 30 clomiphene citrate resistant PCOS patients from EL Shatby maternity hospital. Hormonal profile including; FSH, LH, free testosterone, AMH and progesterone was done preoperatively and 3 months after LOD. **Results:** After LOD 19/30 cases (63.3%) had spontaneous ovulation. After LOD the mean AMH decreased significantly from 9.12 ng/ml to 7.66 ng/ml (p = 0.006*). Responders had significantly lower preoperative AMH as compared to non-responders (8.01 ng/ml Vs 10.01 ng/ml). Responders had a highly significant (p < 0.01) decrease in AMH post LOD while non-responders did not have a significant change in AMH level in responders. While in non-responders there was no significant change in AMH after LOD. Using ROC curve, pre-treatment AMH level of 7.7 ng/ml is a moderate predictor for patients who ovulated after LOD. **Conclusion:** Measurement of serum AMH concentration before LOD may be a useful tool in predicting responders to LOD and help in patient selection.

Keywords

Polycystic Ovarian Syndrome, AMH, LOD

1. Introduction

Polycystic ovarian syndrome (PCOS) is the most common pathologic cause of menstrual disturbance in females in the reproductive age. Its exact etiology is still unknown; however there are multiple risk factors in addition to polygenetic inheritance as the syndrome runs in families [1].

Anti-Mullerian hormone (AMH) is a dimeric glycoprotein, which is secreted by granulosa cells of primary, pre-antral and small antral follicles (4 - 6 mm). AMH is one of the most accurate markers of ovarian reserve as it reflects the quantity and activity of recruitable follicles [2].

It was found that PCOS patients have high AMH and the severity of the endocrinal abnormalities in these patients is positively correlated to AMH levels. High AMH inhibits follicular recruitment via its effect on FSH-receptors as well as inhibition of the follicular aromatase enzyme. Moreover, high AMH is a poor prognostic marker for medical or surgical treatment modalities for PCOS patients. So, any measure that decreases AMH may improve ovulation in these patients [3] [4].

Laparoscopic ovarian diathermy (LOD) is considered as a second line therapy for clomiphene citrate resistant PCOS patients. It has always been thought that LOD works by destroying ovarian stroma which reduces intraovarian androgens leading to a more physiologic estrogenic follicular microenvironment [5] [6].

2. Aim of the Study

The study aims at finding the effect of laparoscopic ovarian drilling on AMH and to evaluate the possibility of using postoperative changes of AMH as a predictor of success of LOD.

3. Study Design

Case series.

4. Patients

The study was conducted on 30 clomiphene citrate resistant PCOS patients attending the infertility clinic of El-Shatby Maternity University Hospital. Inclusion criteria were; patients complaining of primary infertility and aged between 20 and 35 years. PCOS was diagnosed according to Rotterdam's criteria [7]. All patients were resistant to clomiphene citrate ovulation induction. Patients on clomiphene citrate and/or metformin should wait for at least 3 months before being recruited in the study.

Exclusion criteria were; patients with previous history of ovarian surgery and those having multiple infertility factors.

5. Method

All patients signed an informed consent and were subjected to complete history taking and examination and assessment of infertility factors. PCOS was diagnosed according to Rotterdam's criteria.

Basal hormonal assessment was done on cycle day 3 (spontaneous or induced cycle) which included FSH, LH, free testosterone and AMH. Progesterone was measured on day 21. Hormonal profile was done twice; 1 month before LOD and 3 months after LOD. Assays for FSH, LH, testosterone and progesterone were performed by automated micro particle enzyme-immunoassay. AMH was measured by quantitative enzyme linked immunoassay kit, samples were taken one month before and three months post-operative either spontaneous or induced cycle. The sensitivity of the assay was 0.24 ng/ml. The intra and Inter-assay variabilities were, 5% and 8%, respectively.

laparoscopic ovarian drilling

Laparoscopic ovarian drilling was done via 3 ports; a 10 mm infra umbilical port and two 5mm lateral ancillary ports in lower abdomen just above the anterior superior illac spine lateral to inferior epigastric vessels. Inspection of the pelvis is carried out to rule out other factors of infertility. Chromotubation is done by trans-cervical injection of methylene blue dye.

The drilling is performed using an insulated unipolar electro cautery needle electrode. The uninsulated part of the needle is 8 mm long and its diameter is <1 mm. The needle is inserted into the ovarian surface as close to perpendicularly as possible. The whole length of the bare area of the needle is inserted into the ovary and is activated for 2 - 3 seconds with 40 Watt of coagulating current at each point. Total of 5 punctures per ovary were done. After drilling, the ovary was left to cool down in a pool of saline to prevent excessive heat trauma.

Statistical analysis of the data

Data were fed to the computer using IBM SPSS software package version 20.0.

Qualitative data were described using number and percent.

Quantitative data were described using mean and standard deviation, minimum and maximum.

For normally distributed data, comparison between two independent populations was done using independent t-test. Correlations between two quantitative variables were assessed using Pearson coefficient.

Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

a: Mean value $\left(\bar{X}\right)=\frac{X}{n}$.

where X = the sum of all observations.

n = the number of observations.

b: The standard deviation S.D. = $\sqrt{\frac{\sum\left(X-\bar{X}\right)^2}{n-1}}$

where

$\sum S\left(X_i-X\right)^2$ = the sum of squares of differences of observations from the mean.

6. Results

The study was carried on 30 infertile PCOS patients. The mean age was 27.63

(S.D. 3.84) and the mean BMI was 26.6 (S.D. 2.49). Within three months after LOD, 19 cases ovulated spontaneously (63.3%), while 11 cases showed no response (36.7%) (Table 1 and Figure 1).

Preoperative and postoperative hormonal profile is showed in Table 2. We could not find a significant change in FSH nor LH after LOD. However, there was a significant increase in day 21 progesterone after LOD. After LOD the mean AMH decreased significantly from 9.12 ng/ml to 7.66 ng/ml (p = 0.006*). Dividing the studied group into responders and non-responders according to the occurrence of spontaneous ovulation after LOD, showed that the fall in

Table 1. Demographic, clinical and basic hormonal profile.

	Mean	Standard deviation
Age	27.63	3.84
BMI	26.6	2.49
Duration of infertility (years)	3.6	1.5
Basal FSH (mIU/mL)	7.4	0.255
Basal LH (IU/L)	11.8	1.28
Progesterone day 21 (ng/ml)	0.79	0.107
AMH (ng/ml)	9.12	3.98

FSH: Follicle stimulating hormone, LH: Luteinizing hormone.

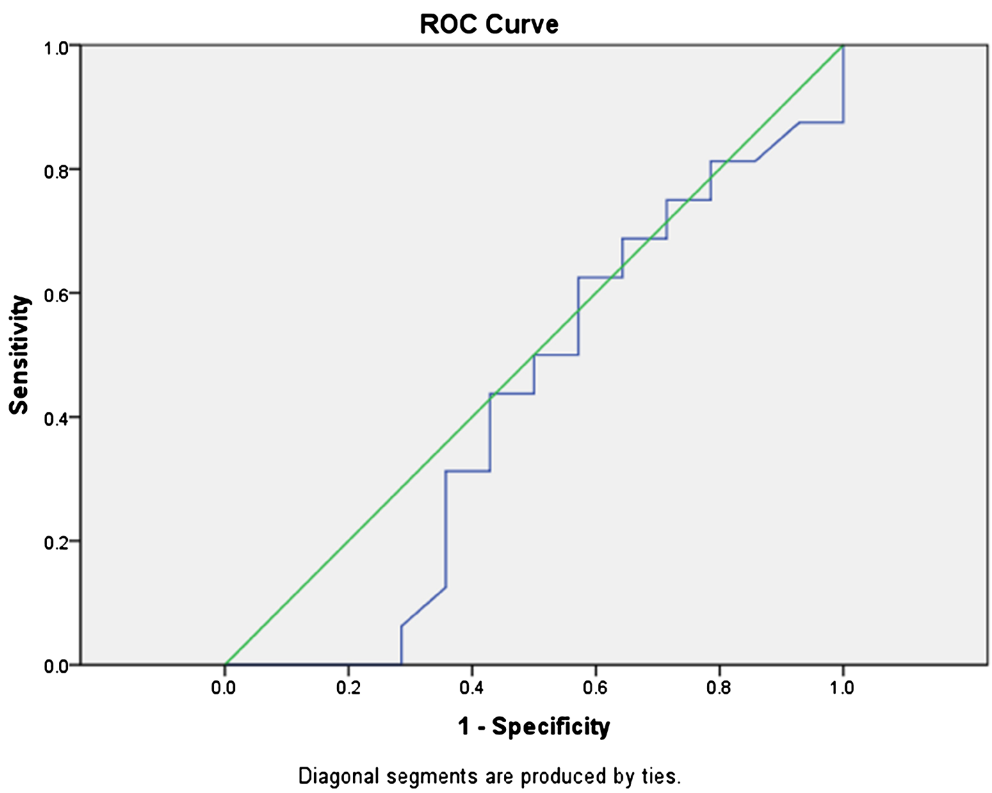

Figure 1. ROC curve to determine the sensitivity and specificity of AMH in detecting the ovulation after LOD.

AMH was highly significant in responders ($p < 0.01$). While in non-responders there was no significant change in AMH after LOD.

Table 3 shows the comparison between the hormonal profile of responders and non-responders to LOD. The prelaparoscopic mean AMH was significantly lower in responders (8.01 ng/ml) than non-responders (10.01 ng/ml). Moreover, the postlaparoscopic AMH was also lower in the responders as compared to non-responders. In addition, responders had a significantly lower prelaparoscopic and postlaparoscopic LH and postlaparoscopic testosterone levels.

7. Discussion

Oral ovulation induction agents are the first line therapy in PCOS patients;

Table 2. Hormonal changes after LOD.

	Pre LOD	Post LOD	P
FSH (mIU/mL)			
Range	7.2 - 8.00	6.8 - 7.22	0.236
Mean	7.4	7.01	
S.D.	0.255	0.65	
LH (IU/L)			
Range	10.00 - 13.90	10 - 12.9	0.521
Mean	11.8	10.6	
S.D.	1.28	1.08	
Progesterone day 21 (ng/ml)			
Range	0.60 - 0.98	3.1 - 28.2	0.001*
Mean	0.79	14.25	
S.D.	0.107	6.98	
AMH(ng/ml)			
Range	6.2 - 21.6	1.5 - 14.2	0.006*
Mean	9.12	7.66	
S.D.	3.98	4.25	

Table 3. Prelaparoscopic and postlaparoscopic hormonal profile in responders and non-responders.

	Responders (n= 19) Mean (SD)	Non-responders (n=11) Mean (SD)	p
AMH(ng/ml) before LOD	8.01 (4.6)	10.01 (3.65)	0.0036*
AMH (ng/ml) after LOD	4.22 (3.98)	10.5 (4.25)	0.0111*
FSH (mIU/mL) before LOD	5.62 (1.89)	4.9 (1.79)	0.107
FSH (mIU/mL) after LOD	5.01 (2.11)	4.55 (1.69)	0.236
LH (IU/L) before LOD	11.6 (5.06)	15.1 (4.98)	0.002*
LH (IU/L) after LOD	8.1 (5.65)	15.6 (3.8)	0.001*
Testosterone (ng/ml) before LOD	2.6 (1.31)	2.85 (1.41)	0.132
Testosterone (ng/ml) after LOD	2.1 (0.85)	3.01 (0.97)	0.045*

however patients who failed to respond can either be treated medically with gonadotropins ovulation induction or surgically with LOD. Gonadotropin therapy is expensive, requires frequent monitoring and carries the risk of multiple gestation and ovarian hyperstimulation syndrome [8].

After LOD almost two thirds of our patients had spontaneous ovulation (63.3%). Paramu reported 80% spontaneous ovulation rate after LOD. In our study, patients who responded to LOD had a preoperative significantly lower AMH than those who were resistant to LOD ($p = 0.0036$). Abu Hashim published a review of literature in 2015 aiming at answering the question "what type of patients would benefit most from ovarian drilling?". He found that obese patients (BMI >25 kg/m) with low basal LH (<10 IU/L) and those with high androgens levels (testosterone levels ≥ 4.5 nmol/L, free androgen index > 15) are less likely to ovulate after LOD. He also concluded that those with infertility less than 3 years and having AMH less than 7.7 ng/mL would benefit more from LOD [9] [10].

In our study, we evaluated the prognostic value of serum AMH for occurrence of spontaneous ovulation in women with PCOS undergoing LOD. The area under the curve identified a cut-off level of AMH (7.7 ng/ml), above which the chances of ovulation seem to be significantly reduced. In agreement with our study, Amer *et al.*, found that at a cut off level of AMH of 7.7 ng/ml had a sensitivity of 78% and a specificity of 76% in the prediction of ovulation after LOD. In a previous retrospective study by the same group on 200 patients with anovulatory PCOS who underwent LOD they found that a AMH 8.5 ng/ml or higher was associated with no ovulation after LOD (sensitivity 74% and specificity 69%) [11] [12].

LOD led to a decrease in AMH in both responders and non-responders however, only in the responder group this fall was statistically significant. So, we concluded that unless a significant fall in AMH, PCOS patients would not benefit from LOD. It is possible that the extent of follicular destruction by LOD in these women was not enough to reduce intra-ovarian AMH to a level that leads to resumption of ovulation.

Paramu, had high ovulation rates after LOD, however, 58.33% of his patients did not get pregnant. These patients had a significantly less decrease in AMH after LOD. So, he postulated that if ovarian tissue destruction is too mild to induce a decrease in intraovarian AMH, LOD will be ineffective. He concluded that the fall in AMH occurring after LOD should be considered as normalization rather than pathological decrease in ovarian reserve. The ineffectiveness of too mild ovarian injury during LOD is also supported by a recent Cochrane review that concluded performing LOD with four to five punctures per ovary is more effective than doing just two or fewer punctures [9] [5].

A retrospective study compared long term effect on ovarian reserve after medical or surgical management of adolescent PCSOS patients was done in 2015. The study was done on a group of PCOS patients who underwent surgical management of adolescent PCOS (34-bilateral ovarian drilling and 22-ovarian wedge resection) and the control group of PCOS patients who did not do any ovarian surgery. The study was done after more than 20 years of the surgical intervention. They found a significantly higher FSH and lower AMH levels in the surgically managed group (p = 0.02 and p = 0.04, respectively). However, looking accurately at the figures the mean AMH at the time of study was 1.6 (±1.5) ng/ml in the surgically managed group which is quite normal considering that the mean age of these patients was 41.6 (±3.5) years [13].

An earlier review of literature by Api concluded that reduction of ovarian reserve after LOD is a step towards normalization of ovarian reserve in these patients and that there is no association between LOD and premature ovarian failure. His conclusion was based on the finding that after LOD ovarian reserve markers in PCOS patients are still more than those of normal subjects [14].

Regarding other hormonal changes, we did not find a significant change in FSH level after LOD. Amer *et al.*, had the same finding too. In addition, in our group of patients LOD did not change androgen levels significantly however, Sunj *et al.* found a significant change in testosterone level after LOD and they even concluded that the change in testosterone level after LOD is an accurate prognostic marker [11] [15].

LOD may be done unilateral or bilateral. A recent metanalysis of 8 randomized controlled trials compared the effectiveness of unilateral versus bilateral ovarian drilling. They found that both are equally effective regarding ovulation rate, pregnancy rates, miscarriage rate and live birth rate. Moreover, both techniques led to a significant decrease in AMH and this reduction was comparable [16].

Yarci Gursoy *et al.*, tried to correlate energy dose used in drilling to the degree of drop in AMH using an animal model. They used 3 different levels of energy on rats. They concluded that the relationship between the energy and AMH could not be documented yet but using very high energy levels led to significant reduction in AMH [17].

Another technique of ovarian drilling is via using the transvaginal route. A randomized clinical trial compared ultrasound-guided transvaginal ovarian needle drilling to the classic laparoscopic ovarian drilling. The study was done on 246 clomiphene citrate resistant PCOS patients. 3 months after the procedures both groups had significantly lower AMH and comparable pregnancy rates. However, the laparoscopic group had a more significant decrease in AMH and higher ovulation rates. 6 months after the procedures, the laparoscopic group proved to be more effective as the ovulation rates and pregnancy rates were significantly higher than those of the transvaginal route, but the fall in AMH was also more significant in the laparoscopic group. The group concluded that the vaginal route is less invasive and safe procedure, but its effect weans within 6 months and its effect on ovarian reserve is milder and transient [18].

So, from our data and from the data of the above-mentioned authors, it is possible to hypothesize that normal levels of AMH are necessary to achieve optimal ovarian responsiveness to ovulation induction. Both too low and too high levels of AMH seem to hinder ovulation. Our data clearly showed that in those patients who responded to LOD, they had a more than 25% reduction in serum AMH level three months post operatively. This reduction of AMH could be the result of destruction of some small follicles (which are the only source of AMH) during the procedure. So, it could be hypothesized that the fall in AMH resulting from LOD could lead to an increase in follicular responsiveness to circulating FSH, thus allowing further growth and selection of a dominant follicle. Alternatively, the post-operative reduction of AMH could be the result of atresia of several small follicles as part of normal follicular development leading to ovulation. So, the observed fall in AMH could be the result, rather than the cause, of ovulation after LOD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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