

## Using preoperative ovarian reserve tests, patients' age and BMI to refine the eligibility criteria for LOD to avoid iatrogenic diminished ovarian reserve

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**Abstract: Overview:** Polycystic ovary syndrome is one of the most common causes of female infertility. According to Rotterdam Criteria, the syndrome is diagnosed by 2 or more of the following: Oligo/Anovulation, Clinical or chemical hyperandrogenism and Ultrasound features; presence of 12 or more arrested follicles ranging from 2-9 mm and/or ovarian volume more than 10 cc. Treatment options include hormonal ovulation induction and laparoscopic ovarian drilling, (LOD). LOD has been widely used to treat the syndrome. It uses electro cautery power to puncture the ovary at different points for the purpose of reducing number of arrested follicles and thus helping ovulation to resume. Although the hopeful results of the procedure in ovulation induction, a lot of debate about the harmful effects of electrocautery on ovarian reserve. **Aim of the work:** This study aims to find the best cutoff value for patients undergoing LOD to avoid insulting their ovarian reserve and thus refining the eligibility criteria for LOD. **Conclusion:** ovarian reserve assessed by hormonal levels and sonography seems to be lower in patients with PCOS undergo LOD.

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**Key Words:** PCOS, LOD, Ovarian reserve, AMH

### 1. Background and Introduction

The polycystic ovarian syndrome (PCOS) is the commonest endocrine disturbance affects women. It is a heterogeneous collection of signs and symptoms gathered to form a spectrum of reproductive, endocrine and metabolic dysfunction. Until recently, there was no international consensus either on the definition of the syndrome 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<sup>(1)</sup>:

1. Oligo- and/or anovulation.
2. Hyperandrogenism (clinical and/or biochemical).
3. Ultrasonographic features of PCOS. The ultrasonographic features of PCOS has been defined as an ovary with 12 or more follicles measuring 2-9 mm in diameter and/or increased ovarian volume more than 10 cm<sup>3</sup>.

PCOS is treated by different methods of ovulation induction, most commonly clomiphene citrate and gonadotropins as well as LOD, which has replaced the more invasive and damaging technique of ovarian wedge resection. Ovarian drilling appears to be as effective as routine gonadotropin therapy in the treatment of clomipheneresistant PCOS. In 50% of LOD treated women, adjuvant therapy will be required. In these women, the addition of clomiphene

citrate after 12 weeks or gonadotropins therapy after 6 months, if there is no evidence of ovulation<sup>(2)</sup>.

The exact mechanism of ovulation induction of LOD is unknown, but it's thought that LOD uses electro cautery to puncture the thick ovarian capsule and the arrested follicles, which is responsible for the hyper estrogenic state, thus helping gonadotropins to return to its normal levels and eventually ovulation resumes<sup>(3)</sup>.

The use of electro cautery power in the ovary has the risk of damaging the remaining primordial and preantral follicles, the ovarian reserve. Diminished ovarian reserve, DOR after LOD is a matter of debate while many studies reported DOR after LOD, other studies negated it<sup>(4)</sup>.

Ovarian reserve tests are used to assess the quantity and quality of primordial and preantral follicles. The most commonly used tests are basal FSH and LH levels, basal antral follicles count and ovarian volume and, most recently, Anti-Mullerian hormone, AMH. Although there is no well randomized clinical studies, AMH is currently considered the best indicator of ovarian reserve. Many researchers said that AMH should be the first test used to measure the ovarian reserve<sup>(5)</sup>.

Maternal age has significant effect on ovarian reserve. Many studies was carried out to find the relation between maternal age and IVF/ICSI cycles outcomes as well as live birth rates. Demographic studies reported that female fertility declines after age of 30, this decline is more rapid after age of 36. In a

study of general infertile population, age was found to be an important prognostic factor for pregnancy rate, for women with a normal ovarian reserve (based on a normal clomiphene citrate challenge test result), but women with diminished ovarian reserve (DOR) were seen to have a poor prognosis independently of age. this study concluded that maternal age and ovarian reserve screening should be combined when counselling patients regarding their prognosis for conception<sup>(6)</sup>.

During a woman's life, ovarian volume changes from 0.7 cm<sup>3</sup> at the age of 10 years, to 5.8 cm<sup>3</sup> at the age of 28 years. However, at the age of 40 years the ovaries tend to decrease in size, and they decrease even further even after menopause. The largest published study of ovarian volume related to age showed a statistically significant decrease in ovarian volume with each decade of life from 30 to 70 years. The mean ovarian volume was 6.6 ± 0.19 cm<sup>3</sup> in women less than 30 years of age; 6.1 ± 0.06 cm<sup>3</sup> in women 30–39; 4.8 ± 0.03 cm<sup>3</sup> in women 40–49; 2.6 ± 0.01 cm<sup>3</sup> in women 50–59; 2.1 ± 0.01 cm<sup>3</sup> in women 60–69; and 1.8 ± 0.08 cm<sup>3</sup> in women ≥70. Mean ovarian volume was 4.9 ± 0.03 cm<sup>3</sup> in premenopausal women and 2.2 ± 0.01 cm<sup>3</sup> in postmenopausal women<sup>(7)</sup>.

As we have shown, this steady decrease in ovarian volume throughout reproductive life significantly correlates with the number of primordial follicles present in the ovary. Women who have a mean ovarian volume of less than 3 cm<sup>3</sup> have a very high chance of failure to respond to ovulation induction, implying significantly reduced ovarian reserve. These women were found to have high cancellation rate in ART cycles. However, it is not a good test to predict pregnancy<sup>(8)</sup>.

## 2. Patients and Methods

### Participants

This study is a prospective cohort study which was carried out at Obstetrics and Gynecology department, Aswan University Hospitals over a period of 1 year. 50 primary infertile PCOS patients were recruited who were attending at out outpatient infertility clinic and whose ages were less than 40 years old. We used Rotterdam criteria to diagnose PCOS as it's the most widely accepted. Any patient with previous ovarian surgery was excluded as it may have negative impact on ovarian reserve. Patients with preoperative DOR were excluded as well.

Data collection involved detailed patients' history and reviewing medical records. Preoperative AMH, patients' ages, patients' BMI and preoperative ovarian volume were used as potential indicator for poor outcomes, diminished ovarian reserve,( DOR. )

### Procedures

We assessed patients' ovarian reserve preoperatively using serum AMH level and basal ovarian volume. Basal ovarian volume was measured for each patient on day 1-5 of the cycle, by a 10 MHz transvaginal ultrasound probe, then we calculated the volume using the prolate ellipsoid formula;  $\frac{4}{3} \pi \frac{a*b*c}{8}$  where a, b and c are length, width and depth of the ovary respectively. We calculated the mean ovarian volume for each patient; sum of ovarian volume divided by 2. All patients had their BMI measured by using the BMI formula:  $\frac{\text{Weightinkg}}{\text{Heightinmeters}^2}$ .

All patients underwent bilateral LOD with fixed settings; 40 watts monopolar diathermy power, 4 punctures each one is 4 seconds long. These setting were recommended by many laparoscopy experts to avoid extensive ovarian damage however there is no evidence supporting this claim<sup>(9)</sup>. At 3 months postoperative, we assessed patients' ovarian reserve by AMH level.

### Data collection

Detailed history were taken from all patients at the infertility clinic with focusing on the diagnostic criteria of PCOS; cycle regulation, weight gain and hirsutism and previous history of ovarian surgery. All patients had their BMI measured as well. Data of pre- and post- operative serum levels of AMH and ovarian volume were collected from lab and ultrasound reports respectively. Postoperatively, patients were grouped according to their postoperative AMH level, patients with AMH equals to 1 or more were considered normal, while patients with AMH is less than 1 were considered DOR patients.

### Statistical analysis

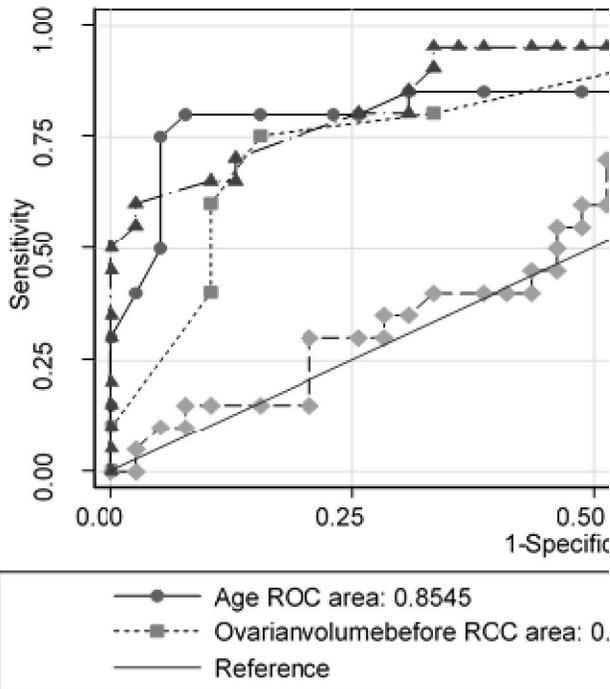
We used preoperative BMI, ovarian volume and AMH as predictors of DOR. For each preoperative measure we calculated sensitivity, specificity, odds ratio likelihood ratio at different cut off levels. A receiver operator characteristics, ROC curves were plotted for the three measures to compare their discriminatory power and accuracy in prediction. ROC also used to choose the best cut off value for each predictor. All data were analyzed using IBM<sup>®</sup> SPSS<sup>®</sup> V.20 software.

### 3. Results

As shown from Table 1, the mean age of the patients was 28.11±6.08, while their BMI had a mean of 28.13±4.04. Ovarian volume before the operation had a mean of 9.96±2.03, while the mean serum AMH level before the operation was 3.94±1.59. Patients' serum AMH levels were calculated 3 months after the operation and had a mean of

1.8±1.17 while postoperative ovarian volume had a mean of 7.59±1.54.

As shown from

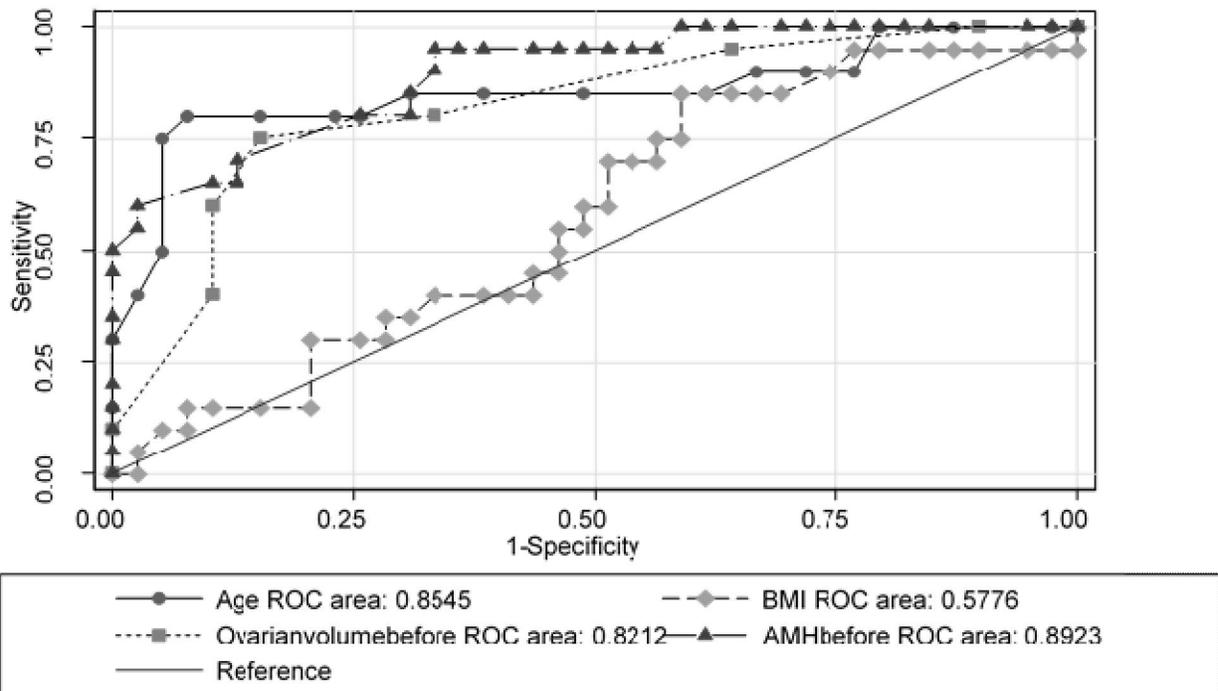


volume as indicators of poor outcomes; DOR. We used the 3 months postoperative AMH as the gold standard test to diagnose DOR cases. Sensitivity and specificity analysis were calculated for the most accurate cut-off value of each preoperative measure.

Figure /Error! Reference source not found., Receiver Operator Characteristic curves, ROC curves were generated for each preoperative measure; Age, BMI, preoperative AMH and preoperative ovarian

**Table 1: summary of patients' data**

	Mean (±SD)	Median (range)
<b>Age</b>	28.11 (6.08)	27 (18-59)
<b>BMI</b>	28.13 (4.04)	29.1 (19.5-34.7)
<b>Ovarian volume before</b>	9.96 (2.03)	11 (6-13)
<b>Ovarian volume after</b>	7.59 (1.54)	8 (5-11)
<b>AMH before</b>	3.94 (1.59)	3.4 (1.08-7.1)
<b>AMH after</b>	1.80 (1.17)	1.8 (0.5-5.8)



**Figure 1: ROC curves for the preoperative measures**

**Table 2: Comparison between AUC, sensitivity and specificity of the preoperative measures**

Factor	AUC (95% CI)	Cut-off	Sensitivity	Specificity	Accuracy
Age	0.85 (0.74-0.93)	>31	80.0%	92.3%	72%
BMI	0.58 (0.44-0.71)	≤31.2	75.0%	41.0%	16%
Ovarian volume	0.82 (0.70-0.91)	≤9	75.0%	84.6%	60%
AMH	0.89 (0.78-0.96)	≤3.5	0.95%	66.7%	62%

As shown from Table 2, ROC curve for patients' preoperative AMH levels had area under the curve, AUC of 0.89 (5% CI was 0.78-0.96) which means excellent discriminatory test for predicting poor outcomes. Sensitivity and specificity were 95% and 66.7% respectively for AMH cut-off point at 3.5, the most accurate cut-off point of the test (Accuracy was 62%). This means that use of AMH cut-off point at 3.5 as preoperative indicator of poor outcomes had good sensitivity and poor specificity, which infers a good positive test.

The second most effective discriminatory measure for predicting poor outcomes was patient's ages which had AUC of ROC curve at 0.85 (95% CI was 0.74-0.93). Age of 31 or more, the most accurate cut-off point, had sensitivity and specificity of 80%

and 92.3% respectively (accuracy was 72%). This means that this test is more specific than sensitive.

Preoperative ovarian volume came on rank three as a predictor of poor outcomes, where its ROC curve had AUC of 0.82 (95% CI was 0.7-0.91). Sensitivity and specificity for the most accurate cut-off point at 9 were 75% and 84.9% respectively (accuracy was 60%), which deducts that the test is also more specific than sensitive.

The least discriminatory test for predicting poor outcomes was the BMI, which had an AUC of its ROC at 0.58 (95% CI was 0.44-0.71). This means that the test is a very weak predictor of poor outcomes. At BMI of 31.2, the most accurate cut-off point, the sensitivity and specificity were 75% and 41% respectively (accuracy was 16%), which obviously shows a very poor specificity.

**Table 3: Odds ratio of the cut-off points of the preoperative measures**

	Odds ratio (95% CI)	P value
Age>31	39.40 (9.60-239.80)	<0.0001
BMI≤31.2	2.08 (0.63-6.90)	0.23

<b>Ovarian volume ≤9</b>	16.5 (4.34-62.67)	<0.0001
<b>AMH ≤3.5</b>	41.07 (4.57-316.02)	0.001

Table 3 shows that odds ratios for AMH cut-off point at 3.5 was 41.07 (95 % CI was 40.57-316.02, *p* value was <0.001) which means strong correlation with poor outcomes. Odds ratio for patients' ages cut-off point at 31 was 39.4 (95% CI was 9.6-239.8, *p* value was <0.0001) which also infers significant correlation with poor outcomes. Preoperative ovarian volume cut-off point at 9 had less strong contribution to postoperative poor outcomes as its odds ratio was 16.5 (95% CI was 4.34-62.67, *p* value was < 0.0001). On the other hand, BMI cut-off point at 31.2 had the least significant correlation with poor outcomes as its odds ratio was 2.08 (95% CI was 0.63-6.9, *p* value was 0.23).

The above results infer that the best predictor for postoperative DOR is AMH at 3.5 or less followed by Age at 31 or more and preoperative ovarian volume at 9 or less. This means that these patients are not candidates for LOD. On the other hand using BMI at 31.2 or less has no correlation with poor outcomes.

#### 4. Discussion

PCOS is the most common cause of ovarian factor infertility, it's characterized by oligo/anovulation, hyperandrogenic state, presence of multiple arrested ovarian follicles and increased ovarian volume. It's also associated with DM, obesity and metabolic syndrome.

There are several ways to treat PCOS including ovarian stimulation protocols as well as LOD. LOD uses electrocautery power to stimulate the arrested ovary to resume ovulation. Studies confirmed that it's as equivalent as gonadotropins stimulation protocols in treatment of clomiphene citrate resistant patients. Nevertheless, the use of electric power in the ovaries increased the debate about iatrogenic diminished ovarian reserve.

Ovarian reserve is defines as the quantity and quality of the remaining preantral follicles in the ovary. Ovarian reserve tests comprises ovarian volume, antral follicles count, basal FSH/LH, AMH and many other tests. They all aim to give an idea about the fertility potential of the female reproductive system.

The current study was conducted at obstetrics and gynecology department, Aswan University on 50 patients complaining of primary infertility due to

PCOS aiming to predict poor outcomes in PCOS undergoing LOD.

Our study showed decrease in AMH level after LOD from 3.9±1.6 to 1.8±1.2 as well as ovarian volume from 9.96±2.03 to 7.59±1.54. These results are consistent with Api (2009)<sup>(10)</sup>.

Also consistent with Weerakiet *et al.* (2007) (11) who concluded that AMH levels seemed to be lower in the LOD (4.60 +/- 3.16 ng/ml) than in the PCOS without LOD (5.99 +/- 3.36 ng/ml) groups, but did not reach statistical significance. Day-3 FSH levels were significantly higher and AFC was significantly lower in the LOD than in the PCOS group without LOD.

Also agree with Elmashad (2011)(12) who found that Plasma AMH and ovarian stromal blood flow Doppler indices were significantly reduced in the PCOS group after LOD. Women who ovulated after LOD had a significantly lower preoperative AMH compared with the nonresponders. There was a significant positive correlation between AMH and power Doppler flow indices before and after LOD in PCOS group.

In this study age at 31 or more and preoperative ovarian volume at 9 or less, these patients are not candidates for LOD. On the other hand using BMI at 31.2 or less has no correlation with poor outcomes. These results disagree with Weerakiet *e tal.* (2007) (11) who resulted that There were no differences in age and body mass index between groups (PCOS with and without laparoscopic ovarian drilling).

#### 5. Conclusion

This study showed that ovarian reserve assessed by hormonal levels and sonography seems to be lower in patients with PCOS undergo LOD.

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