

Risk Factors for Anti Mullerian Hormone Decline after Laparoscopic Excision of Endometrioma: A Prospective Study

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Abstract

Background: Laparoscopic excision of ovarian endometrioma is believed to decrease the ovarian reserve, but the risk factors of declining ovarian reserve are not well studied. This study aimed to determine the risk factors of anti mullerian hormone (AMH) decline after laparoscopic surgery of endometrioma.

Materials and Methods: This prospective study was recruited in Yas and Arash Hospitals affiliated to Tehran University of Medical Sciences from 2020 to 2021. Women between 18-45 years with ovarian endometriomas with a diameter greater than 3 centimeters who were candidates for laparoscopy were included. AMH, luteinizing hormone (LH), and follicular stimulating hormone (FSH) as well as cancer antigen 125 (CA125) and cancer antigen 19-9 (CA19-9) were obtained and compared pre and postoperatively. Indeed, the relation of AMH decline rate and the demographic, symptoms and endometrioma characteristics were investigated either.

Results: In this study, 100 women were recruited. The mean \pm SD age of the participants was 29.08 ± 4.6 . AMH ($P < 0.000$) and LH ($P = 0.013$) declined significantly postoperatively. Whereas, no significant difference was observed between pre and postoperative FSH ($P = 0.520$). AMH decline rate was $30.07 \pm 2.30\%$ and didn't have significant relation with the demographic characteristics, preoperative AMH, and the amount of CA125. Otherwise in the multivariate analysis, CA125 ($P = 0.160$) and the grade of endometriosis ($P = 0.05$) had significant correlation with AMH decline rate.

Conclusion: Ovarian reserve decline after laparoscopic excision of endometrioma. Otherwise, there may no specific risk factor to predict the degree of ovarian reserve decline. Therefore, the selection of patients for laparoscopic excision of endometrioma should be taken more cautiously as the ovarian reserve diminishes even in the patients with the lowest risks.

Keywords: Anti Mullerian Hormone, Endometrioma, Laparoscopy, Ovarian Reserve

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Introduction

Endometriosis is a common disease affecting about 10% of women of reproductive age. Ovarian endometriomas could be found in 17-44% of these patients which shows no symptoms in up to 50% of the cases (1-3). There is no accurate statistics in Iran but it seems near to 60% of the infertile couples in Iran had endometriosis (4). For many years, the first line therapeutic approach to these cysts was laparoscopic surgery (5, 6). Since endometriomas lack a true capsule separating the cyst from the ovarian tissue, it is inevitable to excise the cyst without cutting some of the normal tissue of the ovary. The point of question and worrisome in this approach is the damage to the ovarian reserve as a result of unintentionally excised normal ovarian tissue (7, 8).

Ovarian reserve is a potential predictor of a female's reproductive system and is based on the number and eventual quality of the ovum. In the last three decades, the level of anti mullerian hormone (AMH) (9), follicular stimulating hormone (FSH), estradiol (E2) and inhibin B as well as the ovarian volume and the antral follicular count (AFC) on transvaginal sonography have been accepted as reliable markers of ovarian reserve (10-12), among which AMH is the most attractive due to its ease of measurement and independency to the menstrual cycle (1, 13, 14).

Different studies have proved ovarian reserve decline after laparoscopic excision of endometriomas assessing all or some of the aforementioned markers. In some studies

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cyst diameter, cyst bilateralism, preoperative AMH and patient's age were shown to be relative to the degree of ovarian reserve decline. Meanwhile, other studies proved wise versa (15-18).

This study designed to find any risk factors that make it possible to predict which patients may have higher declines in ovarian reserve postoperatively using ovarian decline rate as a marker showing the degree of the damage to the ovarian reserve and to give a more precise guide in cautious choice of patients for laparoscopy.

Materials and Methods

Population

This prospective study was conducted in Yas and Arash Hospitals affiliated to the Tehran University of Medical Sciences. All participants signed the written informed consent and were eager to participate in the study. Women with ovarian endometrioma between 18 to 44 years old who were planned for laparoscopic excision of the endometrioma between July 2020 and January 2021 were included. The exclusion criteria were a history of previous adnexal surgery, hormonal replacement therapy, and endocrine disorder, ovarian mass suspicious for malignancy, polycystic ovaries and endometriomas of less than 3 centimeters diameter.

This study was approved by the institutional review board Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1399.272). The protocol of the study was designed according to the ethical principles of the Declaration of Helsinki. All participants agreed to participate in the study and the written informed consent was obtained from all participants.

Sample size calculation

The sample size that was required with a power of 95 was 70 cases, of which 100 cases were considered for this study.

$$n = \frac{2\left(\left(z_1 - \frac{\alpha}{2}\right) + (z_1 - \beta)\right)^2 p' q'}{(p_1 - p_2)^2}$$

p1: Preoperative AMH
p2: Postoperative AMH

$$z_1 - \alpha/2 = 1.96$$

$$z_1 - \beta = 0.84$$

Study conduct and objectives

The demographic (age, weight, height, age of menarche, marital state) and obstetrical data (gravid and para), as well as the clinical symptoms (dysmenorrhea, dyspareunia, persistent pelvic pain, dysphasia, fear of sex) and history of infertility for female cause were gathered via a questionnaire that was filled by a physician or a nursing staff. Also, ultrasound imaging was done for

each patient to see the precise diameter of the cysts and their laterality status. Patients also underwent laboratory testing for the level of FSH, LH, AMH, CA125 and CA 19-9 pre and 3 months post operatively.

Also, a new variable was created as AMH decline rate calculated by the below formula. AMH decline rate is a new variable to assess any correlation between the severity of the damage to the ovarian reserve and any of the other independent variables hypothesized as possible risk factors.

$$\text{AMH Decline rate} = \frac{\text{preoperative AMH} - \text{postoperative AMH}}{\text{Preoperative AMH}} \times 100$$

Laparoscopic excision of ovarian endometrioma

All the procedures were performed by two expert laparoscopic surgeons with more than 15 years of experience in laparoscopic surgery, whose procedures were to excise the cyst by stripping, avoiding to damage ovarian normal tissue as much as possible.

Statistical analysis

All the data were analyzed by the software package for social sciences (SPSS, IBM, USA) for windows version 15.0. Quantitative values were presented as mean \pm SD and qualitative values were presented as absolute and relative frequency. Chi-Square test was used to assessed statistical relations of qualitative variables. Comparison between the groups was performed using Mann-Whitney U test. Friedman M test was used to compare the differences of serum AMH concentrations between each sampling point and the changes of serum AMH levels For quantitative variables we used ANOVA and t test. Also for decreases the potential bias, multivariate analysis was performed to evaluate the AMH decline rate with other characteristics. $P < 0.05$ was considered to be statically significant.

Results

One hundred patients were included in the study. The mean \pm SD age of the patients and menarche were 29.08 ± 4.6 (with a range of 19-41) and 12.56 ± 1.35 years respectively. The characteristics of the patients with endometriomas preoperatively are listed in Table 1. Also the frequency of the clinical symptoms and the mean of BMI and hormonal profiles in the participants are listed in Table 2. As seen, dysmenorrhea is the most prevalent symptom in these women.

AMH levels decreased significantly 3 months after surgery ($P < 0.000$). The mean \pm SD of AMH decline rate was calculated to be $30.07 \pm 2.30\%$ among all patients. LH levels also declined significantly ($P = 0.013$) but there were no significant changes between the levels of FSH pre and postoperatively ($P = 0.527$). There was no correlation between patients' characteristics, preoperative AMH and CA125 with AMH decline rate (Table 3).

Table 1: Characteristics of the patients with endometriomas undergoing laparoscopy (n=100)

Charchteristics		n (%)	Mean ± SD	P value
Age (Y)	>35	8 (8)	28.92 ± 13.6	0.78
	≤35	92 (92)	30.22 ± 23.98	
Laterality of cysts	Unilateral	45 (45)	30.24 ± 23.97	0.948
	Bilateral	55 (55)	29.94 ± 22.45	
Cyst size (mm)	≤70	52 (52)	31.28 ± 22.17	0.602
	>70	48 (48)	28.87 ± 24.01	
Endometriosis	Stage III	58 (58)	24.27 ± 24.36	0.002
	Stage IV	42 (42)	38.09 ± 18.48	
Dysmenorrhea	Yes	88 (88)	30.08 ± 22.85	0.99
	No	12 (12)	30.00 ± 25.37	
Dyspareunia	Yes	43 (62.3)*	30.1 ± 24.74	0.63
	No	26 (37.7)	24.41 ± 20.61	
Persistent pelvic pain	Yes	34 (34)*	30.24 ± 23.71	0.96
	No	66 (66)	29.99 ± 22.85	
Dyschezia	Yes	29 (29)	26.96 ± 22.64	0.38
	No	71 (71)	31.35 ± 23.22	
Infertility	Yes	40 (59)	27.21 ± 24.8	0.434
	No	29 (42)	31.67 ± 20.81	

*; Calculated in married cases. SD; standard deviation

Table 2: Frequency of clinical symptoms and the mean of BMI and hormonal profiles in the participants

Charchteristics	n (%) or Mean ± SD
Dysmenorrhea	88 (88)*
Dyspareunia	43 (62.3)**
Persistent pelvic pain	34 (34)*
Dyschezia	29 (29) *
Fear of sex	16 (23.2)**
BMI (kg/m ²)	22.6 ± 2.0
FSH (IU/L)	6.66 ± 1.43
LH (IU/L)	7.43 ± 1.61
CA 125 (U/ml)	141.9 ± 104.6
CA 19-9 (U/ml)	44.15 ± 22.7

; Percentage among 100 patients (married and unmarried), **; Percentage among 69 married patients, BMI; Body mass index, FSH; Follicle stimulating hormone, LH; Luteinizing hormone, CA 125; Cancer antigen 125, and CA 19-9; Cancer antigen 19-9.

Table 3: Correlation of the rate of AMH decline rate with patient's characteristics and lab data

Variable	Correlation	P value
Age (Y)	-0.017	0.873
Menarche (Y)	-0.045	0.654
BMI (kg/m ²)	-0.120	0.235
AMH (ng/ml) (preoperative)	0.163	0.106
CA125 (U/ml)	-0.099	0.329

BMI; Body mass index, AMH; Anti mullerian hormone, and CA 125; Cancer antigen 125.

In linear regression please the R and the relations of other factors with the outcome and their R quantity is listed in Table 4.

Table 4: The R square and adjusted R square for the laterality of the ovarian cyst and hormones

R square	Adjusted R square	Standard error of the estimate
0.209	0.101	20.59523

And at last, the multivariate analysis between the potential predictors and AMH decline rate is shown in Table 5. As seen just CA 125 (P=0.160) and the grade of endometriosis (P=0.05) had significant correlation with AMH decline rate.

Table 5: Multivariate analysis between the potential predictors and AMH decline rate

Model	Unstandardized coefficients		Standardized coefficients	T value	P value
	β*	Standard error			
Constant	-7.836	39.945		-0.196	0.845
Age (Y)	0.128	0.618	0.029	0.208	0.836
BMI (kg/m ²)	0.266	1.149	0.025	0.231	0.818
Menarch	0.148	1.650	0.009	0.090	0.929
Cyst size (cm)	0.095	0.125	0.087	0.756	0.452
AMH preop (ng/ml)	7.444	3.931	0.245	1.894	0.062
CA19-9 (U/ml)	0.112	0.104	0.118	1.075	0.286
CA125 (U/ml)	-0.057	0.023	-0.286	-2.477	0.016
FSH preop (IU/L)	-1.123	1.568	-0.077	-0.716	0.476
Grade of endometriosis	13.945	4.787	0.321	2.913	0.005
Cyst laterality	-1.142	4.696	-0.026	-0.243	0.809

β; Unstandardized beta, BMI; Body mass index, AMH; Anti mullerian hormone, and FSH; Follicular stimulating hormone.

Discussion

Endometriosis is an obscure disease defined by extrauterine growth of endometrial tissue. Ovaries are one of the most prevalent sites for endometriosis to be found. Laparoscopic excision of endometriomas for long was accepted as the first line therapeutic approach in these cysts (6, 7), but the decreased number of the ovum's obtained through IVF cycles after endometrioma cyst excision, gave rise to some worrisome about this approach (19).

In the present study, a significant decline in AMH level as a marker of ovarian reserve was observed three months postoperatively. This indirectly addresses the inevitable damage to the ovarian reserve with the surgery of these cysts. Different characteristics of endometriomas can lead to ovarian reserve decrease. Indeed, the AMH level declined postoperatively especially large and bilateral endometriomas (20). In another study AMH decreased significantly at 1, 3 and 6 months after surgery, although, no difference was detected from preoperative and AMH values at 12 months (21). Otherwise, Sugita et al. detected no significant difference 12 months after surgery (22). Also the result of Goodman et al. study was interesting

that showed AMH levels have recovered in 12 months after a transient decrease (23).

FSH levels did not increase significantly according to the diminished AMH levels, this has also been explained in previous studies as FSH seems to be a less sensitive marker in determining the changes of the ovarian reserve and its level does not increase significantly until premenopausal years.

In another study, the only risk factor proved to be related to the severity of AMH decline rate was the patients' preoperative level of AMH, which was not proved in our study (24). Indeed, cyst diameter of greater than 4 centimeters was proved to be a predictor of higher AMH decline rates postoperatively (25) and finally cyst diameter ≥ 7 centimeters, cyst bilateralism, preoperative AMH level and patients age were introduced to be effective and relative risk factors for greater decline in ovarian reserve (19). Otherwise, none of the mentioned items were proved in our study.

Regarding the importance of cyst size, in our study, we found no correlation with AMH decline. However, the literature is controversial. In one study the decline in AMH at 6 months after surgery was more evident in the patients with larger endometriomas (>5 cm) (26). Otherwise A meta-analysis showed the greater endometrioma may lead to the greater damage to ovarian reserves which leads to a decrease in serum AMH levels (27).

Regarding the importance of laterality we found no significant difference in post operative AMH levels in patients with bilateral compared to unilateral. This is in line with Suardi et al. study that serum AMH levels were not influenced by their laterality (28).

The limitation of our study is the short follow up duration. Therefore further studies with longer follow up and investigation of the effect of surgery on the fertility rate with a focus on AMH are recommended. Also the non-significant findings in the current study could also be caused by the small number of the participants.

Conclusion

Since the present study like other studies has shown a significant decline in AMH levels postoperatively, while none of the independent variables were found as a risk factor or predictor of the rate of this decline, we can conclude that probably surgical intervention even in patients with the lowest risks can result in diminished ovarian reserve. This conclusion makes it necessary to select patients for surgical intervention more cautiously at any age or with any clinical and paraclinical presentation.

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Authors' Contributions

All authors contributed to this work and were involved in designing the study, data collection, and writing the manuscript. All authors read and approved the final manuscript.

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