Association of Endometrioma Size with Serum Anti-mullerian Hormone

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ABSTRACT

Objective: To evaluate the relationship between the size of endometrioma and serum Anti-mullerian hormone (AMH).

Study Design: A Descriptive study.

Place and Duration of Study: This study was conducted at the Bagcilar Training and Research Hospital, Istanbul, Turkey, from January 2015 to January 2020.

Methodology: Healthy women of reproductive age, who were found to have unilateral endometrioma in ultrasonography, were included in the study group. There were 82 female patients with unilateral endometrioma in the study group and 96 healthy female patients with male factor infertility in the control group. Women with autoimmune disease, a history of pelvic infection or surgery, polycystic ovary syndrome, pregnancy, those undergoing infertility treatment, family history of premature ovarian failure, and those with atypical or suspected endometrioma were excluded. Age, gravida, serum AMH value, and endometrioma size of the study and control groups were recorded. In addition, the endometrioma group was divided into 2 groups with a cut-off size of greater or less than 40 mm. AMH values were evaluated in these two groups.

Results: AMH values of women with endometrioma were significantly lower than the control group (2.03 ng/ml and 3.87 ng/ml, respectively, $p<0.001$). When the relationship between endometrioma size (greater than 40 mm and less than 40 mm) and AMH was examined, no statistically significant difference was found among serum AMH values (1.89 ng/ml and 2.07 ng/ml, respectively, $p=0.65$).

Conclusion: The presence of endometrioma was associated with lower AMH suggesting lower ovarian reserve, but endometrioma size was not associated with significant difference in the AMH values.

Key Words: *Endometrioma, AMH, Ovarian reserve, Endometrioma size.*

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INTRODUCTION

Endometriosis is a chronic inflammatory disease that occurs when endometrial tissue (stroma and gland) is located outside the uterine cavity. It is seen in 2-10% of women of reproductive age.[1] It is most commonly located in the pelvis and 17-44% of the women with endometriosis have ovarian endometriosis.[2]

Endometrioma is a disease that occupies space in the ovary and causes inflammation in the surrounding tissue, thus reducing the quality and number of the oocytes. It has been shown that the presence of endometrioma is associated with the decreased ovarian reserve, and ovarian reserve decreases further with the surgical treatment.[3]

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Today, one of the most frequently used tests to understand the reserve is serum Anti-mullerian hormone (AMH) levels. AMH is a glycoprotein secreted by primordial cells. It can be expected that the compression of the primordial cells in the wall of the endometrioma and the resulting inflammation will decrease by directly affecting the secretion of AMH secreted from these cells. It has been shown in many studies that endometrioma surgery and removal of the endometrioma reduce ovarian reserve. However, data on only the presence of endometrioma effect on ovarian reserve are limited. Endometriosis has recently been treated with expectant, medical, and surgical treatment. In addition to the follow-up of current endometriosis in women of reproductive age, the most important fear is the possible decrease in ovarian reserve. It is understood that the presence of endometrioma reduces the ovarian reserve, but there is insufficient data to compare the damage to the ovary occurring between large-sizes and small-sizes as the cyst grows. In this study, the authors evaluated the effect of endometrioma and the size of the endometrioma on the ovarian reserve without surgery.

METHODOLOGY

This retrospective study was performed with the permission of the clinical research ethics committee of Istanbul Medipol University, dated 17/06/2021, and numbered 673. The study included 82 women with unilateral endometrioma aged 20-38 years, who were followed up in the endometriosis outpatient clinic of Istanbul Bagcilar Training and Research Hospital, between January 2015 and January 2020, and 96 secondary infertile women who were treated for male factor infertility in the infertility outpatient clinic of the same centre. The patients' characteristic including age and history of pregnancy were collected using the İnternational Classification Data-base (ICD) codes from the electronic medical database of the hospital. The patients were divided into two groups as women with and without endometrioma.

Women with autoimmune disease, a history of pelvic infection, or surgery, polycystic ovary syndrome, pregnancy, those undergoing infertility treatment, with a family history of premature ovarian failure, and patients with atypical or suspected endometrioma, were excluded from the study.

For the diagnosis of endometrioma, trans-vaginal ultrasonography (TVUSG) was performed on sexually active patients, and trans-abdominal ultrasonography (TAUSG) was performed on virgo women. All the patients were evaluated using the Esaote MYylab™ X7 vaginal probe and 5 MHz convex probe ultrasonography device. Round-ovarian cysts that persisted, for at least 2 months, were larger than 10 mm, thick walls, regular borders, had homogeneous-hypoechoic internal echoes, and had no papillary structure and heterogeneous internal echoes, were recorded as endometrioma.[4] The largest external to external diameter of the endometrioma cyst walls was recorded in centimetres. Patients with endometrioma were divided into 2 groups *i.e.* those with smaller than 40 mm and larger than 40 mm. The patients in the control group were evaluated for any ovarian cyst in their first examination, after confirming that there was no cyst, blood was taken for serum AMH value on the day of measurement by ultrasonography regardless of the cycle day. The serum AMH level was measured by the Elica technique (Roche E411, USA).

Women with and without endometrioma were compared in terms of the serum AMH levels. In addition, women with endometrioma smaller than 40 mm and in diameter were compared to the women with larger endometriomas.

IBM SPSS version 20 (Chicago, IL, USA) program was used in the evaluations. Mean standard deviation, median, and IQR values were given in descriptive statistics for continuous data, and number and percentage values were given in discrete data. Kolmogorov-Smirnov test was used to examine the conformity of continuous data with normal distribution. Since the AMH value did not fit the normal distribution; therefore, used the Mann-Whitney U test for comparison and gave the median and IQR values as descriptors. T-test was used because the age value fits the normal distribution. Kruskal-Wallis analysis of variance was used in the comparison between the AMH values of the cyst group and the healthy individuals with cyst sizes >40 mm and <40 mm. Kruskal-Wallis pairwise comparisons test was used as post hoc test to understand which group or groups caused the difference. Chi-square and Fisher's exact tests were used for the group comparisons of nominal variables. A $p < 0.05$ was accepted as statistically significant.

RESULTS

A total of 178 patients were included in this study. The patients were divided into two groups, 96 patients in the control group (53.9%) and 82 patients (46.1%) with unilateral endometrioma cyst group. The patients in the study were between 20-38 years old, and there was no significant age difference between the two groups (29.32±5.01 and 30.58±3.94, respectively, p=0.066) (Table I).

Table I: Characteristics of the patients with endometrioma cysts.

	Endometrioma group (n=82)	Control group (n=96)	p-value
Age	29.32±5.01	30.58±3.94	0.066*
Age group n (%)			
≤35 years	72 (87.8)	86 (89.5)	0.708***
>35 years	10 (12.2)	10 (10.4)	
AMH median (IQR)	2.03 (1.14-4.50)	3.87 (2.10-5.92)	<0.001**

** Independent Samples t-test; ** Mann-Whitney U test; *** Chi-Square test.*

Table II: Comparison of patients' characteristics and AMH values in patients with endometrioma cysts.

	AMH Median (IQR)	p-value
Age		
≤35 years	2.14 (1.14-4.47)	0.865*
>35 years	1.84 (1.34-6.10)	
Previous pregnancy		
No	2.07 (1.29-4.98)	0.350*
Yes	1.84 (0.75-3.82)	
Endometrioma group		
≤40 mm	1.89 (0.84-3.63)	0.646
>40 mm	2.07 (1.15-5.21)	

** Mann-Whitney U test.*

In the endometrioma group, the median cyst size was 41.5 mm (11mm - 65 mm). While 88% (72 patients) of the patients in the cyst group were younger than 35 years old, only 10 patients were older than 35 years. There were an equal number of patients older than 35 years in the control group. There was no difference in the AMH values between the patients aged 35 years and younger and patients older than 35 years (p=0.87, Table II).

About one-third (30 patients) in the cyst group had previously been pregnant. There was no difference between in the AMH values of the patients with a previous pregnancy history and the patients who had never been pregnant (p=0.35, Table II).

The serum AMH value of the patients in the cyst group was lower than the AMH value of the patients in the control group (2.03 ng/ml, min-max 1.14 - 4.50 and 3.87 ng/ml, min-max 2.10 - 5.92) (p<0.001, Table I).

The endometrioma size was found to be over 40 mm in approximately half of the women (42 patients) in the cyst group. There was no difference between the serum AMH values of patients with small and large cysts (1.89 ng/ml and 2.07ng/ml, respectively) (p=0.65, Table II).

A significant difference was found between the AMH values of those with cyst smaller than 40 mm and larger than 40 mm in the healthy individuals (p=0.001). In the multiple comparison test, the serum AMH levels of the patients in both endometrioma groups were found to be significantly lower than the control group (p=0.003 and p=0.037, respectively).

DISCUSSION

Ovarian reserve is a concept related to the number and quality of oocytes remaining in both ovaries. A good ovarian reserve test should be able to demonstrate a woman's current and future reproductive performance and capacity to produce steroid hormones. For the evaluation of ovarian reserve, AMH, antral follicle count (AFC), serum follicle-stimulating hormone (FSH) level, and estradiol measurement were performed on one of the 2nd, 3rd, and 4th menstruation days are used. The number of oocytes retrieved in women undergoing assisted reproductive technology is also a reserve indicator.

AFC is not useful for reserve assessment in the ovary with endometrioma. AMH was also used as a reserve test, because there may be an incorrect or insufficient count owing to decrease in the image quality of TVUSG/TAUSG and the inability to visualise some antral follicles due to the cyst. In the literature, AMH is recommended for ovarian reserve control in the follow-up of patients with endometriosis.[5,6] AMH is a reliable test that does not show intercyclic and intracyclic changes, easy to perform, and has a threshold value for evaluation.[7]

In this study, the relationship between endometrioma size and ovarian reserve was evaluated. The authors accepted 4 cm as the cut-off, which is widely accepted in the literature. In the literature, it has been shown that the presence of an endometrioma smaller than 4 cm does not impair the result in patients undergoing IVF, and ovarian damage is more common in the surgery for an endometrioma larger than 4 cm.[8] In 2014, with the decision of the ASRM committee, follow-up was recommended for the cysts smaller than 5 cm with endometrioma features.[9] The effect of surgical treatment on the ovarian reserve is evident, especially in cysts larger than 4 cm.[10]

The women with endometrioma are very important in two ways; first, if woman is infertile, a decision that directly affects pregnancy performance is to be made, such as the choice of drug and method to be used in infertility treatment and the adjustment of drug doses, or if there is no desire to have children, treatment may need to be planned due to early ovarian dysfunction and clinical symptoms. AMH seems to be the most robust marker to evaluate ovarian reserve in the women with endometrioma. In this study, the effect of endometrioma on ovarian reserve by comparing the AMH levels between healthy women of equal age and women with endometrioma are measured. In the current publications, there are conflicting results showing that the AMH value decreases, increases, or does not change in the presence of endometrioma. As a result, it is found that the presence of endometrioma reduces ovarian reserve, but the reserve is not lower in larger ones. Endometrioma is a disease that causes inflammation and compression in the surrounding tissue, changes the local vascular and lymphatic circulation, and affects cytokines. Explaining this is not easy with the available information. If ovarian endometriosis is present, the antral follicles continue to exist, but the AMH production may be reduced due to cyst compaction and inflammation. However, AMH decreases in women undergoing surgical resection due to loss of antral follicles. With surgical resection, the AMH production may continue to decrease as the antral follicles are not reduced and simply under pressure. If follow these patients both by ultrasonography and by looking at AMH levels in the 1st, 2nd, and later years, it can be determined whether the endometrioma has a progressive damage. Yes, there is harm, but the important thing is to be able to predict the effect of this damage on clinical folliculogenesis.

In the literature, the results of the studies investigating the effect of endometrioma on the AMH level are contradictory. Although there is a large literature data showing that AMH decreases due to endometrioma, there are also publications showing that the endometrioma does not affect on ovarian reserve. In 2012, Streuli *et al*., in their prospective study with 4-year data and a large number of patients, showed that although the patients had some biases due to their previous endometriosis surgery history, deep infiltrative endometriosis, ovarian cyst surgery history, and a non-ideal control group, endometrioma did not decrease AMH.[11] In a meta-analysis including 17 studies published in 2018, the AMH values of 968 women with endometrioma and 1874 women without endometrioma were compared, and the AMH values were lower in the endometrioma group than in the control groups.[12] This review explained the correlation with the results of this study. There are low AMH levels indicating decreased ovarian reserve in the presence of endometrioma. There are no comments regarding the size of the endometrioma. Obtained AMH results suggest that size does not matter in this study. Whereas, in the comparison of 64 patients in the control group and 118 women with endometrioma, it was found that AMH did not decrease in patients with endometrioma, and there was no relationship between endometrioma size and AMH, but in this study, age was not compatible between the study group and the control group, and patients with multiple endometriomas were not separated with the clear boundaries.[13] In a study published in 2021 comparing 22 women with endometrioma and a control group consisting of 22 women without endometrioma, it was found to be lower in the presence of AMH endometriosis, although it was not statistically significant.[14] Contrary to these studies, Marcellin *et al*. compared the AMH value of 148 women with endometrioma and 119 women with non-endometrioma ovarian cysts, they reported that the AMH value was higher in women with large endometrioma than the control group, and

they attributed this to an increased ovarian toxic effect with increasing endometrioma diameter.[15], Roman *et al*. reported that increasing endometrioma size and AMH value showed a positive correlation.[16] In this study, lower AMH values in the presence of endometrioma than in the control group are found. However, the authors obtained lower AMH values in 40 mm and smaller endometriomas than in women with 40 mm endometriomas, but the difference was not statistically significant.

The important limitations of this study are that it is retrospective and the number of patients is small. However, the strength of this study is that those who had bilateral endometrioma and ovarian surgery were excluded from the study and only unilateral cases were included.

The aim is to question the confidence in a test showing that endometrioma reduces ovarian reserve. If interpret according to the results, the damage caused by endometriosis and endometrioma to the ovary is not a progressive condition, because it is not dependent on the size of the ovary.

CONCLUSION

According to the results of this study, the AMH value in women with endometrioma is lower than in women without endometrioma, regardless of the size of the endometrioma. The fact that the increase in the endometrioma size does not decrease serum AMH level, correlation should be confirmed by the studies with larger case numbers. However, surgery in these patients further decreases the ovarian reserve: therefore, surgical treatment should be avoided unless there are severe clinical complaints. Malignancy is suspected in my ultrasonographic appearance, and it is not necessary for the infertility treatment.

ETHICAL APPROVAL:

This retrospective study was performed with the permission of the clinical research ethics committee of Istanbul Medipol University, dated 17/06/2021, and numbered 673. We obtained ethical approval prior to the initiation of the research work.

PATIENTS' CONSENT:

Informed consent was obtained from the patients to publish data for this study.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

OKA: Created and planned the working hypothesis, worked on data collection, statistical analysis, and interpretation.
HG, EEK, TK, TOA, TC: Worked on data evaluation, interpretation, literature search, and manuscript writing.
All the authors have approved the final version of the manuscript to be published.

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