



# Laparoscopic Cystectomy of Endometrioma Outcomes on Follicle Stimulating Hormone and Anti-Müllerian Hormone Levels as Predictors of the Ovarian Reserve

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## Abstract

**Objectives:** This study aimed to examine the effect of a laparoscopic cystectomy on ovarian reserve assessed by measuring the levels of serum follicle stimulating hormone (FSH) and anti-Müllerian hormone (AMH).

**Materials and Methods:** This prospective, analytical study measured the changes of basal FSH and AMH in endometrioma patients undergoing laparoscopic cystectomy in Dr. Hasan Sadikin Hospital from June to August 2016. An informed written consent was obtained from all patients prior to the study. Their FSH and AMH serum levels were examined one month before and after the surgery.

**Results:** A total of 31 patients were included in the study and divided into two groups based on two age ranges of 20-35 years (n=16) and 36-42 years (n=15). It was found that the FSH serum levels increased whereas the AMH serum levels decreased in both groups after laparoscopic cystectomy ( $P<0.001$ ).

**Conclusions:** Laparoscopic cystectomy of patients with reduced endometrioma ovarian reserve was characterized by elevation of FSH serum levels and reduction of AMH serum levels.

**Keywords:** Anti-Müllerian hormone, Cystectomy, Endometrioma, Follicle stimulating hormone, Laparoscopy, Ovarian reserve

## Introduction

Endometriosis is a common gynecologic disease found among nearly 5% to 15% women in their reproductive age, and 3 to 5% women in the post-menopause period (1,2). Few studies have investigated the patients suffering from endometriosis in Indonesia; according to the available data, however, endometriosis is nearly 13.6% among infertility cases in Dr. Moewardi General Hospital, around 37.2% in Dr. Soetomo General Hospital, and 69.5% in Dr. Cipto Mangunkusumo General Hospital (unpublished data).

Majority of patients suffering from endometriosis are also afflicted with endometrioma (3). Endometrioma is a common cause of infertility due to pelvic anatomy distortion, fallopian tubes obstruction, ovulation and implantation disruption, immunological reaction, as well as oocyte quality reduction due to impairment of folliculogenesis (4-6). Current treatment modalities are focused on surgery, including laparoscopy. Laparoscopic cystectomy is one of the treatments for patients with endometrioma; however, it could result in reducing ovarian reserve due to the damaged healthy ovarian tissue during cyst wall dissection (7,8). The damage affecting healthy ovarian tissue decreases the ovarian reserve, which is

indicated by the rise of basal follicle stimulating hormone (FSH) levels and the reduction of anti-Müllerian hormone (AMH). Both hormones are indicators of the reduced ovarian reserve (9-11). This study aimed to examine the effect of laparoscopic cystectomy of endometrioma on the ovarian reserve by comparing the differences between FSH and AMH serum levels one month before and after the surgery.

## Materials and Methods

This study was an analytic prospective study with pre-post design, aiming to reveal the effect of laparoscopy endometrioma cystectomy on ovarian reserve. It was conducted in Dr. Hasan Sadikin General Hospital and in several private hospitals in Bandung city, Indonesia from June to August 2016.

The study subjects were women having unilateral endometrioma with diameter 4 cm and the following characteristics: reproductive age (i.e., 20–42 years old), regular menstrual cycle, normal body mass index (BMI), no history of prior endometrioma surgery, and not receiving hormonal therapy before and after surgery. Patients with bilateral endometrioma, malignancy, endocrine abnormalities, and premature ovarian failure



## Key Messages

- ▶ Endometriosis is a common gynecologic disorder and laparoscopic cystectomy is a method of choice in treating endometrioma.
- ▶ Laparoscopic cystectomy of endometriomas will increase FSH and decrease AMH levels.

(FSH>25 IU/mL) were excluded. The sample size was obtained using sample size calculator for paired t-test. The minimum sample size was estimated to be 15 subjects.

The blood samples for FSH measurement were taken from the vein on the second day of the menstrual cycle before surgery, and on the second day of menstrual cycle one month after the surgery. Examination of the FSH levels was conducted using enzyme-linked fluorescent assay. On the other hand, examination of the AMH levels was carried out using enzyme-linked immune-absorbent assay.

### Statistical Analysis

The data were analyzed by SPSS version 21 for Windows. A normality test for numeric variables was performed using the Shapiro-Wilk test. Descriptive statistics were used to describe the patient demographics. McNemar test was used for analyzing categorical variables, while paired t-test and Wilcoxon signed-rank test were performed accordingly.

### Results

A total of 31 women were included in this study. Demographic characteristics of the patients were as follows: age range of 20-41 years, normal BMI, cysts between 4-9 cm with a median of 6 cm, and duration of infertility range of 2-10 years with a median of four years (Table 1).

As the FSH levels increased after the surgery, the AMH levels decreased. The mean FSH serum level prior to the surgery was 6.77 IU/L, but it was 8.12 IU/L after surgery ( $P<0.001$ ). The mean of AMH serum levels prior to surgery and after surgery were 1.43 ng/mL and 0.94 ng/mL, respectively ( $P<0.001$ ) (Table 2).

### Discussion

In this study, the subjects were divided into two age groups including “20-35 year-old reproductive group” and “36-42 year-old group”, since the mean of normal value of ovarian hormones in each group was different (12). The 20-35 age group consisted of 16 subjects while the 36-42 age group included 15 subjects, and the mean of age was 32.7 years old. This finding was consistent with the results from the literature suggesting that endometriosis was a gynecological disorder affecting 10-15% of women in reproductive age. Endometrioma is found in 17-44% of women with endometriosis (13).

**Table 1.** Demographic Characteristics of Participants (n = 31)

Variables	Mean (SD)	Median	Range
Age (y)	32.7 (5.5)	34	20-41
BMI (kg/m <sup>2</sup> )	20.8 (1.4)	21	19-23
Size of cysts (cm)	5.8 (1.7)	6	4-9
Duration of infertility (y)	4.7 (2.5)	4	2-10

**Table 2.** Comparison of FSH and AMH Level Prior to and Following Surgery

Variables	Observation		P Value
	Prior	Following	
FSH (IU/L)			
Mean (SD)	6.77 (3.10)	8.12 (2.95)	<0.001
Range	2.26-13.25	3.37-14.01	
AMH (ng/mL)			
Mean (SD)	1.43 (0.62)	0.94 (0.50)	<0.001
Range	0.4-3.0	0.1-2.2	

The mean BMI in this study was 20.8, and women's fertility was affected by their body weight and BMI. Obesity and overweight had effects on women's reproductive health. Obesity causes irregular menstrual cycle and anovulation, reduces the chance of conception, and triggers unfavorable response to infertility therapy. In a study by Parveen et al, BMI increase was found associated with a decrease in the ovarian reserve among infertile patients (13). It has been determined that AMH level is significantly correlated and BMI in the group of normal ovarian reserve. In Johnson and Hummelshoj's study, it was shown that the decrease in AMH levels was related to the high BMI score of infertile women with reduced ovarian reserve compared to normal ovarian reserve (12,14-16). Thus, subjects included in our study were women with normal BMI and ranging between 18.5 and 24.

Infertility is another characteristic that has been the focus of several studies. Endometriosis is believed to have a causal relationship with infertility, and is found in 50% sub-fertile women compared to fertile women (5%-10%). Moreover, the fecundity number on a monthly basis is 0.02 to 0.10, compared to 0.15 to 0.20 on fertile couples (15). In this study, the mean duration of infertility was 4.7 years.

Ovarian reserve is the total pool of ovarian follicles, showing the potential fertility of a woman. To date, no method capable of assessing the ovarian reserve accurately has been developed. Many markers have been developed for ovarian reserve measurement. Even though the experts have argued that the number of growing follicles reflects the total follicles, the relationship between these two factors has remained unclear (13). In this study, AMH and FSH were used as measures to predict the ovarian reserve.

The mean of FSH serum levels collected in this study before the surgical procedure was 1.43 ng/mL, and the result was still within the normal limit. Therefore, the

patients underwent laparoscopic cystectomy. As the FSH increased after surgery, the AMH levels decreased. The pre-operative serum FSH was 6.77 IU/L, which significantly increased to 8.12 IU/L after operation ( $P < 0.001$ ).

Several studies have reported that there are more mature follicles and oocytes disposal during endometrioma cystectomy compared to non-endometrioma ovarian cyst cystectomy. This is related to the theory of endometrioma cyst originated from an implant that is invaginated at the ovarian cortex and expanded during the menstrual cycle. Other indicators suggesting a reduced ovarian response after endometrioma cystectomy include longer stimulation period, a higher dose of steroid consumption, lower E2 level, and fewer oocytes taken (17,18).

Other studies have shown that ovaries with endometriosis cysts, compared to other benign cysts, reduce follicles and vascular activities (18). Furthermore, it is difficult to identify the impact of endometrioma alone since most cases are related to peritoneal endometriosis.

The causes of reduced ovarian reserve can only be hypothesized. There are still no definitive data available to clarify whether the damage is associated with surgical procedure and/or with previous presence of a cyst. Thus, the damage to the surrounding ovarian tissue by the cyst cannot be confirmed. Based on histological analysis, it has been reported that the ovarian tissue surrounding the cyst wall in endometriomas may be morphologically altered and may not be functional. Functional disruption may be present before surgery.

In our study, AMH serum level examinations were carried out one month before surgery. The post-operative AMH level measurements were performed on different occasions in various studies. Most studies conducted AMH level measurement three months after surgery, and two studies measured AMH level several times, three and nine months after the surgery, in order to investigate AMH serum level thoroughly. It was determined to be better because the long-term effect on the AMH level may have been examined, while changes within the short-term period may have been transient (13). In this study, a decrease was found in AMH serum levels one month after surgery, which was 34.26% with the mean of pre-operative AMH serum level 1.43 ng/mL ( $P < 0.001$ ) (Table 2). In a study by Raffi et al (12) the reduction of post-operative AMH serum level was 40%. This finding was also in agreement with the result from another study by Mostaejeran et al, reporting a 48% reduction in AMH levels post-endometriosis surgery (19,20).

Many studies have explored the AMH levels, yet the AMH secretion process itself has not been explained scientifically. Zaitoun et al found a decreased AMH level in patients undergoing either unilateral cystectomy or oophorectomy (21). Other researchers demonstrated that the decrease was followed by an increased AMH level after cystectomy with 65% recovery after three months, while some researchers found a continuous decrease six

months after surgery (19-21). AMH level is known to be lower during childhood, even if the ovarian reserve is higher. It is assumed that there are differences between the in-situ AMH production and AMH level serum. The vascular phenomenon, which is of special importance in the operative procedure, might be able to explain the transient long-term variations of AMH levels. The decrease in AMH levels is likely to occur more often in bilateral endometrioma cystectomy (22).

In this study, the increase in FSH serum level one month after surgery reached 19.94% with the mean of pre-operative FSH serum level at 6.77 IU/L and post-operative level at 8.12 IU/L (Table 2). This finding was in line with the study result of Zaitoun et al (21) who compared patients having endometrioma and undergoing laparoscopic cystectomy by bipolar electrocoagulation with patients having endometrioma and undergoing laparotomy cystectomy by suturing. They found a significant increase in FSH serum level of patients who had laparoscopic cystectomy by bipolar electrocoagulation 6, 12, and 18 months after surgery compared to that of patients who had laparotomy by suturing.

The changes in FSH and AMH levels are likely suggestive of the added degree of tissue damage caused by surgery. There is evidence that stripping the cyst tissue from the underlying ovarian stroma also removes the primordial and even the preantral follicles, despite the fact that extreme care is exercised during surgery in order to preserve as much healthy tissue as possible (21).

Busacca et al and Benaglia et al reported that ovarian failure after surgery increased from 2.4% to 13% several months after endometrioma cystectomy (17,23). This may have been attributed to the removal of healthy tissue during cystectomy, vascular disturbances due to electrosurgical coagulation, and an autoimmune reaction due to local inflammation (16).

The advantage of surgical procedure is reduced in women with recurrent endometriosis. This can be caused by several factors such as relapsing endometriosis (often an aggressive disease with poor prognosis) after the first surgery, adhesions due to the first surgery that might interfere pregnancy, and the following surgery that might cause further disturbances to the remaining ovarian reserve (18).

Another study that assessed the impact of endometrioma cystectomy towards pregnancy rate did not include ovarian reserve. The given study identified several factors that affected the fertility. Severe pelvic adhesion, endometriosis in organs other than the ovaries, adenomyosis, and inflammatory substances within peritoneal fluid might influence the pregnancy rate among those undergoing endometrioma cystectomy (16). The best method to assess ovarian reserve in the patients having endometrioma cystectomy is to control ovarian hyper stimulation and evaluate the ovarian response.

Another important issue concerns the side effects of

endometrioma. Although a surgery removes the pathologic lesion, complaints pertaining to endometriosis and/or endometrioma may persist due to incomplete removal of lesions and/or re-emergence of lesions. These complaints include various types of pain, such as menstrual pain, pain with intercourse, and pain with bowel movement and/or urination. Therefore, patient care is not discontinued after surgery. Analgesia and hormonal preparations may be required to manage their long-term side effects (15).

This study faced some limitations. First, a lower number of subjects were included in this study. Despite meeting our sample calculation criteria, a study enjoying a larger population with longer duration may have produced more favorable results. Second limitation concerned the timing of AMH measurement. Different studies had measured AMH values at different time points with supporting arguments for each approach. At the time of this study, there was no agreed-upon approach. As such, a direct comparison of our results with the findings from other studies was out of question. Third, surgical techniques to separate the cyst wall from healthy tissue as well as the technique to stop the ovarium bleeding, which may affect the ovarian reserve, were not adopted in our study. Different techniques could elicit different results and side effects. Therefore, it was recommended that the ovarian reserve should be measured 3, 6, and 9 months after surgery in order to evaluate the changes in FSH and AMH serum levels and Antral Follicular Count using ultrasonography.

This study did not evaluate the relationship between the ovarian reserve and the post-operative pregnancy rate; therefore, conducting a prospective study was found necessary to evaluate such rate. This was particularly consistent with our findings suggesting that the age affected FSH and AMH serum levels, while the length of infertility affected FSH serum level. However, the effects of the surgical techniques on tissue damage and, as a result, on the hormonal level abnormalities are still unknown. Therefore, it was suggested that further studies should be carried out to determine whether the damage was related to the surgical procedure or to the previous presence of a cyst.

## Conclusions

In sum, the surgery for ovarian endometrioma was found a controversial issue. It was recommended that the surgery should be customized according to the patients' complaints, their present situation, and their desire for pregnancy. As for the assessment of the effect of cystectomy laparoscopic on ovarian reserve, it was found that ovarian reserve measured by FSH and AMH levels was significantly decreased after cystectomy laparoscopic endometrioma.

## Authors' Contribution

Study conception: RA, AW, DH. Data collection: AW, DH. Data

analysis: RA, AW, DH, KIM, SMS, TD and WP. Manuscript drafting: RA, DH, KIM, SMS, BH, SK, JE, DN. All authors reviewed the manuscript and agreed upon this final version for publication..

## Conflict of Interests

Authors declare that they have no conflict of interests.

## Ethical Issues

This study was approved by the Health Research Ethics Committee of Hasan Sadikin Hospital through an ethical clearance, and an informed written consent was obtained from all participating respondents prior to the research. Confidentiality was maintained during and after the study, and the subjects were allowed to discontinue their participation at any point during the study.

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