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# **RESEARCH**

# Comparison of Ovarian Reserves Before and After Laparoscopic Cystectomy "Fertility Sparing" in Endometriosis Cyst Patients

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#### Abstract

Laparoscopy Cystectomy still remains the first line as the treatment of endometriosis cyst. A "fertility sparing" laparoscopy is a procedure that preserve uterus and ovaries of endometrioma patient.

**Objective**: was to compare the ovarian reserve before and after laparoscopic cystectomy "fertility sparing" using three marker of ovarian reserve which are AMH, FSH and Estradiol on 2nd or 3rd day of menstrual period and counting the AFC by Transvaginal Ultrasound.

Methods: This study is an experimental study on 25 endometrioma patient. Ovarian reserve values was taken before and after laparoscopy using three markers which are AMH, FSH and Estradiol and AFC. All patient included to group performed laparoscopy cyctectomy with several techniques which are no or less use of electrocoagulation, using vassopresin injected to the cyst wall, using stripping of the membrane technique on cyst, without suturing, using compression to control bleeding, avoiding hillus cut. Statistical Analysis was using paired t test method.

**Result**: There was average differences on AMH value before  $1,77 \pm 0,39$  ng/ml and after laparoscopy  $1,54 \pm 0,38$  ng/ml. FSH value before was  $6,91 \pm 4,59$  mlU/ml and after was  $10,13 \pm 6,51$  mlU/ml, for estradiol before was  $99,65 \pm 77,18$  mlU/ml and after was  $63,67 \pm 35,22$  mlU/ml. There were 15 samples before laparoscopy has AFC <4, 10 samples has AFC 4-6, after laparoscopiy there was 8 samples has 8 AFC, 8 samples has 4-6 AFC, and 9 samples has 7-10 AFC. There was a statistical significance on the reduce of ovarian reserve before and after laparoscopic cystectomy "fertility sparing" (p=0,001). **Conclusion**: There was the affect of laparoscopy cystectomy to the decrease of ovarian reserve which sre 13% decreaed of AMH (p+0,001), 31,6% increased of FSH (p=0,001), estradiol was 47,8% decreaed (p=0,001) and AFC has increased 47.9% (p=0,003).

Keywords: Laparoscopic Cystectomy, Endometriosis, Anti Mullerian Hormone, Antral Follicle

#### INTRODUCTION

Endometriosis is a benign gynecological disease characterized by the presence of stroma and endometrial glands outside the uterine cavity, especially in the pelvic peritoneum, ovaries and rectovaginal septum.<sup>1,2</sup> It usually affects women of reproductive age and is associated with painful menstruation, infertility and decreased quality of life.<sup>3,4</sup> In general, the most

Received: December 5<sup>th</sup>, 2019 Accepted: December 28<sup>th</sup>, 2019



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common sites for endometriosis are the ovaries, peritoneum, rectovaginal septum and ureters, but rarely in the bladder, pericardium and pleura.<sup>2</sup> Women of reproductive age with pelvic pain and infertility have a prevalence of endometriosis around 35-50%. 1,2 The average age of people with endometriosis is about 28 years. <sup>5</sup> The true prevalence of endometriosis is not known because most cases are not detected until about 10 years or late diagnosis due to a latent period of 6-7 years from the onset of the disease. <sup>6,7</sup> The standard for the diagnosis of endometriosis is laparoscopy followed by histopathological examination.<sup>7</sup> Over time, endometriosis increases up to 50% in infertility cases, although the mechanism of infertility due to endometriosis is still uncertain.8 In endometriosis cysts, there is a chronic inflammatory reaction, an increase in apoptotic reactions, decreased immunocellular activity, increased angiogenesis, hormonal imbalance (estrogen-dependent progesterone resistance), etc., which cause damage to the ovarian follicles which have implications for decreasing ovarian reserve. This decrease in ovarian reserve is also accompanied by a decrease in egg quality, a decrease in endometrial receptivity, an increase in rejection reactions to sperm and embryos, an increase in apoptosis in sperm, a disturbance in hormonal balance, all of which lead to infertility.

Laparoscopic cystectomy is a treatment that aims to prevent wider follicular damage and prevent the spread and / or adhesions of the internal genital organs. But the laparoscopic cystectomy itself can also cause removal or damage of healthy follicles, especially the primordial follicles located in the hillus of the ovary. It is difficult to avoid damage to healthy follicles during the laparoscopic cystectomy. The removal of the cyst pocket, especially the hilar area, will cause the removal of normal ovarian tissue containing primordial, primary and secondary follicles. To minimize damage to healthy follicles during laparoscopic cystectomy, experts have carried out various preservation measures on the ovaries, including: prevention of the use of bipolar / monopolar coagulation cautery, proper stripping of the membrane technique, preoperative hormonal therapy (GnRH Analog), use of vasopressin for reduce bleeding, use hemostat agents, make cuts at the base of the cyst (hillus area) to avoid damage to the primordial follicles and so on.

Based on the risk and benefit analysis of endometriosis cystectomy, ESHRE 2013 recommends operative action only for endometriosis cysts with a size of  $\geq$  3cm. The importance of considering the risks and benefits of laparoscopic endometriosis cystectomy in infertile patients is the key to the success of the pregnancy program in relation to the availability of ovarian reserves. For this reason, the researcher wants to apply various preservative measures carried out by other researchers, including: use of vasopressin on the cyst wall, avoiding electrocoagulation, compression techniques on the bleeding area, not forcing the base of the cyst bag in the hilar area (cut), stripping of the membrane. precision,

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and others aimed at reducing the effect of decreasing ovarian reserve without increasing the risk of recurrence.

In this study, ovarian reserve assessments will be carried out before and after the laparoscopic cystectomy by applying the "fertility sparing" technique and analyzing how much influence the cystectomy procedure has on decreasing ovarian reserve.

### **METHOD**

The design of this study is an experimental study, which is a study that examines the effect or impact of risk factors, namely laparoscopic cystectomy on ovarian reserves. This study was conducted in a paired data group, namely checking the ovarian reserve before the laparoscopic cystectomy was performed, then given exposure in the form of cystectomy and then re-checking the ovarian reserve after the procedure. Then an analysis was performed to assess the differences in ovarian reserve before and after the laparoscopic cystectomy. Ovarian reserve assessment is done by checking basal FSH and E2 levels, AFC and AMH levels. The hypothesis used is a pairwise numerical comparative hypothesis. With this study design, it can be seen how much influence or impact of laparoscopic cystectomy using the "fertility sparing" technique on FSH-E2, AFC, AMH before and after laparoscopy.

The research will be conducted at the FER polyclinic RSUP dr.M. Djamil Padang and RSU C-BMC Padang for the period of March - September 2019. Ovarian reserve examination will be examined by immunohistochemistry in the Biomedical Laboratory of the Faculty of Medicine, University of Andalas. Selection of research subjects by determining the target population first, then the reachable population and those that meet the inclusion / exclusion criteria of the reachable population were included in the study sample. Research subjects were female patients diagnosed with endometriosis cysts based on clinical examination and USGTV or Transrectal USG who came to the Reproductive Endocrinology Fertility Polyclinic, dr. M. Djamil Padang and RSU C-BMC Padang who will undergo a laparoscopic cystectomy. The research sample was all affordable populations that met the inclusion and exclusion criteria.

Statistical analysis was used in accordance with the research objectives and hypotheses, namely to determine the degree of decline in ovarian reserves in endometriosis cysts before and after laparoscopic cystectomy. For numerical comparative hypothesis paired data, paired t test is used if it meets the requirements. If it does not meet the requirements, an alternative test is used, namely the Wilcoxon test (nonparametric test). To assess the normality of the data distribution the Shapiro-Wilk test (n <50) was used. Data are presented in the form of mean standard deviation (SD). The significance of the statistical test results was determined based on the p value <0.05. The data obtained were recorded in a special form and then processed by a computer program.

Received: December 5<sup>th</sup>, 2019 Accepted: December 28<sup>th</sup>, 2019



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## **RESULTS**

## **Normality Test**

Normality test is performed using the Shapiro Wilk test to determine whether the data is normally distributed or not.

**Table 1**. Data Normality Test

| Variable                       | n  | Mean ± SD     | p-value |
|--------------------------------|----|---------------|---------|
| AMH                            |    |               |         |
| Before laparoscopic cystectomy | 25 | 1,77 ± 0,39   | 0,05    |
| After laparoscopic cystectomy  | 25 | 1,54 ± 0,38   | 0,30    |
| FSH                            |    |               |         |
| Before laparoscopic cystectomy | 25 | 6,91 ± 4,59   | 0,001   |
| After laparoscopic cystectomy  | 25 | 10,13 ± 6,51  | 0,0001  |
| Estradiol                      |    |               |         |
| Before laparoscopic cystectomy | 25 | 99,65 ± 77,18 | 0,0001  |
| After laparoscopic cystectomy  | 25 | 63,67 ± 35,22 | 0,058   |

Based on Table 1, it is known that AMH levels before and after laparoscopy and estradiol levels after laparoscopy were normally distributed, while FSH levels before and after laparoscopy and estradiol levels before laparoscopy were not normally distributed.

## **Characteristics of Research Respondents**

 Table 2. Characteristics of Research Respondents

| Characteristics                      | Mean ± SD    |   |
|--------------------------------------|--------------|---|
| Age                                  | 30,56 ± 3,72 | _ |
| BMI                                  | 23,50 ± 2,63 |   |
| Marriage history                     |              |   |
| Married                              | 23 (92%)     |   |
| Not yet                              | 2 (8%)       |   |
| Infertile                            |              |   |
| Yes                                  | 22 (88%)     |   |
| No                                   | 3 (12%)      |   |
| History of Laparoscopy or Laparotomy |              |   |
| Yes                                  | 4 (16%)      |   |
| No                                   | 21 (84%)     |   |
| Cyst size > 3cm                      |              |   |
| Yes                                  | 25 (100%)    |   |
| No                                   | 0 (0%)       |   |
| Types of cysts                       |              |   |
| Monolokulare                         | 20 (80%)     |   |
| Multilokulare                        | 5 (20%)      |   |
|                                      |              |   |

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Based on Table 2 it is known that the mean age of the respondents is  $30.56 \pm 3.72$  years and BMI  $23.50 \pm 2.63$ . A total of 23 respondents (92%) were married, experienced infertility, namely 22 respondents (88%), 21 respondents (84%) did not have a history of laparoscopy, all respondents (100%) had a cyst size of more than 3 cm, and 20 respondents (80 %) had a monolocular cyst type.

## **Ovarian Reserve Before Laparoscopic Cystectomy**

**Table 3**. Ovarian Reserve Before Laparoscopic Cystectomy

| Variable        | Before Laparoscopy |
|-----------------|--------------------|
| AMH level       | 1,77 ± 0,39        |
| FSH level       | 6,91 ± 4,59        |
| Estradiol level | 99,65 ± 77,18      |
| AFC             |                    |
| < 4             | 15 (60%)           |
| 4 – 6           | 10 (40%)           |
| 7 – 10          | 0 (0%)             |
| 11 – 30         | 0 (0%)             |
| > 30 0 (0%)     |                    |

Based on Table 3, it is known that the mean AMH levels were  $1.77 \pm 0.39$  ng / ml, FSH levels were  $6.91 \pm 4.59$  mlU / ml, and estradiol levels were  $99.65 \pm 77.18$  mlU / ml before laparoscopic cystectomy. . A total of 15 people (60%) with AFC <4, 10 people (40%) with AFC 4-6, and no patients with AFC 7-10, 11-30, or> 30.

### **Ovarian Reserve After Laparoscopic Cystectomy**

**Table 4**. Ovarian Reserve After Laparoscopic Cystectomy

| Variable        | After Laparoscopy |
|-----------------|-------------------|
| AMH level       | 1,54 ± 0,38       |
| FSH level       | 10,13 ± 6,51      |
| Estradiol level | 63,67 ± 35,22     |
| AFC             |                   |
| < 4             | 8 (32%)           |
| 4 – 6           | 8 (32%)           |
| 7 – 10          | 9 (36%)           |
| 11 – 30         | 0 (0%)            |
| > 30            | 0 (0%)            |

Based on Table 4, it is known that the mean AMH levels are  $1.54 \pm 0.38$  ng / ml, FSH levels are  $10.13 \pm 6.51$  mlU / ml, and estradiol levels are  $63.67 \pm 35.22$  mlU / ml after laparoscopic cystectomy. . A total of 8 people (32%) with AFC <4, 8 people (32%) with AFC 4-6, 9 people (36%) AFC 7-10, and no patients with AFC 11-30 and> 30.

Received: December 5<sup>th</sup>, 2019 Accepted: December 28<sup>th</sup>, 2019



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## **Effect of Laparoscopic Cystectomy on Ovarian Reserves**

**Table 5**. Effect of Laparoscopic Cystectomy on Ovarian Reserves

| Variable        | Before Laparoscopy | After Laparoscopy | p-value |
|-----------------|--------------------|-------------------|---------|
| AMH level       | 1,77 ± 0,39        | 1,54 ± 0,38       | 0,001   |
| FSH level       | 6,91 ± 4,59        | 10,13 ± 6,51      | 0,001   |
| Estradiol level | 99,65 ± 77,18      | 63,67 ± 35,22     | 0,001   |
| AFC             |                    |                   |         |
| < 4             | 15 (60%)           | 8 (32%)           |         |
| 4 – 6           | 10 (40%)           | 8 (32%)           |         |
| 7 – 10          | 0 (0%)             | 9 (36%)           | 0,003   |
| 11 – 30         | 0 (0%)             | 0 (0%)            |         |
| > 30            | 0 (0%)             | 0 (0%)            |         |

Based on Table 5, there is a difference in the mean AMH level where before laparoscopy it was higher, namely  $1.77 \pm 0.39$  ng / ml while after laparoscopy it was  $1.54 \pm 0.38$  ng / ml. There was a difference in the mean FSH level where after laparoscopy it was higher, namely  $10.13 \pm 6.51$  mlU / ml while before laparoscopy it was  $6.91 \pm 4.59$  mlU / ml. There was a difference in the mean level of estradiol where before laparoscopy it was higher, namely  $99.65 \pm 77.18$  mlU / ml while after laparoscopy it was  $63.67 \pm 35.22$  mlU / ml. There is a difference in AFC between before laparoscopy and after laparoscopy where 15 (60%) AFC <4, 10 (40%) AFC 4-6, and no AFC 7-10 before laparoscopy and 8 (32%) AFC < 4, 8 people (32%) AFC 4-6, and 9 people (36%) AFC 7-10 at the time after laparoscopy. Therefore it can be concluded that there is an effect of laparoscopic cystectomy on ovarian reserve.

#### **DISCUSSION**

## **Respondent Characteristics**

The results of this study indicate that the mean age of the respondents is  $30.56 \pm 3.72$  years and the mean BMI is  $23.50 \pm 2.63$ . More than half of the respondents (92%) are married, as many as 88% are infertile, have no history of laparoscopy or laparotomy, 84%, all respondents have a cyst size of more than 3 cm, and 80% have monolocular cyst types.

The results of the study by Chen et al (2014) showed that AMH levels before laparoscopic cystectomy had a significant correlation with patient age, but did not have a significant correlation with BMI, cyst diameter, and unilateral or bilateral cyst types.

Endometriosis is a disorder that is often found in women where the incidence is increasing. Ovarian endometrioma is the most common diagnosis, wherein 17-44% of cases of pelvic endometriosis are present, and the incidence of bilateral ovarian endometrioma increases by 29%.<sup>56</sup> Ovarian endometrioma is benign in that this type of cyst is related to estrogen which is found in 5 to 10% of women of reproductive age. In 20-40% of women who

Received: December 5<sup>th</sup>, 2019 Accepted: December 28<sup>th</sup>, 2019



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experience such cases cause infertility. Women with ovarian endometrioma develop symptoms of dyspareunia, dysmenorrhea, and infertility.<sup>57</sup>

The gold standard for diagnosis and method of treatment in women with symptoms of ovarian endometrioma is laparoscopic cystectomy. However, this technique has a negative effect on ovarian reserve due to removal of normal ovarian tissue. Ovarian reserve describes the number and quality of follicles that remain in the ovary at the time of examination. The method for evaluating ovarian reserve is to determine serum FSH, estradiol, and AMH levels. AMH has the same sensitivity and specificity as AFC, and better than FSH, estradiol, LH, FSH / LH ratio, or inhibin-B levels. If the ovarian reserve decreases, the FSH level increases. In clinical practice, ovarian reserve estimation is done by AFC examination and ovarian volume measurement. 55,57

## **Ovarian Reserve Before Laparoscopic Cystectomy**

Based on the results of this study, it is known that the ovarian reserve before laparoscopic cystectomy is an AMH level of 1.77  $\pm$  0.39 ng / ml, FSH levels of 6.91  $\pm$  4.59 mlU / ml, levels of estradiol 99.65  $\pm$  77.18 mlU / ml. , and 60% of patients with AFC <4.

Until now, there have been many studies discussing the effects of laparoscopic cystectomy on ovarian reserve, but there is still controversy. There are no clear data to clarify that reduced ovarian reserve in patients with endometrioma is associated with surgical procedures, history of endometrioma, or both. In addition, there are no definite risk factors that cause damage to the ovarian reserve after surgery. In this study the researchers compared how the ovarian reserve before and after laparoscopy was performed. The results of this study indicate that the levels of AMH and estradiol before laparoscopic cystectomy were higher.

## **Ovarian Reserve After Laparoscopic Cystectomy**

Based on the results of this study, it is known that ovarian reserves after laparoscopic cystectomy are AMH levels of  $1.54 \pm 0.38$  ng / ml, FSH levels of  $10.13 \pm 6.51$  mlU / ml, levels of estradiol  $63.67 \pm 35.22$  mlU / ml., and 36% of patients with AFC 7-10.

The results of this study are almost the same as the research conducted by Georgievska et al (2014) which states that unilateral laparoscopic cystectomy of ovarian endometrioma decreases ovarian reserve and ovarian volume after surgery. However, ovarian reserve increased again three months after surgery followed by an increase in AFC and estradiol levels. The number of AFC at the time after laparoscopic cystectomy was significantly increased three months later compared to AFC before laparoscopy. FSH levels decreased after three months of follow-up which showed that ovarian reserves were good because the ovaries produced more of the hormone estradiol to inhibit FSH production.<sup>57</sup>

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In Chen et al's (2014) study, it was stated that the group with a cyst size of more than 7 cm experienced a higher reduction in AMH levels after laparoscopy than the group with a cyst size of less than 7 cm (p = 0.001).<sup>55</sup>

## **Effect of Laparoscopic Cystectomy on Ovarian Reserves**

The results of this study indicate that there are differences in ovarian reserve before and after laparoscopic cystectomy. AMH and estradiol levels decreased after laparoscopic cystectomy, while FSH levels increased. The number of patients with AFC <4 decreased after laparoscopic cystectomy from 60% to 32%.

The results of this study are in line with the research of Chen et al (2014) where AMH serum levels decreased one month after laparoscopic cystectomy and there was a significant difference in mean before and after laparoscopic cystectomy. The study compared AMH levels in patients with endometrioma, tubal factor infertility, and other types of benign ovarian tumors. Comparison of the three groups showed a higher reduction in serum AMH levels in patients with endometrioma. From these results it can be assumed that the endometrioma can damage the ovarian reserve. Muzii (2002) reported that ovarian tissue adjacent to an endometrioma often experiences destruction and loss of its characteristic follicular structure, whereas ovarian tissue around other benign ovarian cysts does not. Stilley (2012) states that peritonial macrophages in patients with endometriosis experience dysfunction and can secrete proteinases, harm ovarian tissue and ultimately cause reduced ovarian reserves.

The same thing was also found in the study of Alborzi et al (2013) where AMH levels decreased and FSH levels increased after laparoscopic cystectomy against endometriosis, especially in patients over 38 years of age and with bilateral cysts. AFC levels increased significantly up to three months after surgery. SE Chang et al (2010) stated that the AMH serum level three months after surgery experienced a recovery of about 65% as the condition before surgery. AMH serum levels in the first week after surgery were lower in endometriomas than in non-endometriomas. SE

Revelli et al (2011) reported in their study of the impact of laparoscopic endometrioma on ovarian reserve where it was found that AMH serum levels significantly decreased after surgery (1.4  $\pm$  0.2 ng / ml after 3 months, and 1.3  $\pm$  0 , 3 ng / ml after 9 months) whereas before laparoscopy 3  $\pm$  0.4 ng / ml. However, the concentrations of FSH, LH, E2, and inhibin B did not change. Prior to laparoscopy, AFC was lower in the affected ovary than in healthy ovaries, namely 3.3 and 8.4 and the difference continued for three to nine months postoperatively. AFC in unhealthy ovaries increased three months after laparoscopy compared to before surgery, but did not show a statistically significant association.  $^{60}$ 

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Ercan et al (2011) stated that although laparoscopy affects ovarian reserve in terms of AFC, it does not have a significant negative impact at the end of month 3 as assessed by ovarian volume, Doppler index, and AMH levels. Surgical techniques in managing endometrioma are very important for maintaining normal ovarian function and further research is needed to optimize this surgical technique.<sup>61</sup> Even though endometriosis cystectomy can compromise ovarian reserves, it is still the first choice for treating endometrioma cases.<sup>65</sup>

The results of this study are not in line with research conducted by Adnyana (2018) which states that there is no significant difference in AMH levels before and after the laparoscopic cystectomy stripping technique and partial laparoscopic cystectomy excision. The two techniques show that the partial effect of laparoscopic cystectomy excision on AMH concentration is less than that of stripping laparoscopic cystectomy. AMH levels three months after surgery increased compared to one month after surgery where for laparoscopic stripping cystectomy and partial laparoscopic excision cystectomy one month after surgery 0.98 ng/ml and 1.33 ng/ml increased to 1.29 ng/ml and 1.88 ng/ml. Patients with unilateral and bilateral endometriomas had AMH levels below normal levels and lower AMH levels found in bilateral endometriomas. However, different types of endometrioma did not have a significant impact on AMH levels.<sup>62</sup>

While Zhang CH et al (2016) conducted a study in which there were 207 patients with 13 exclusions who were divided into 3 groups with different laparoscopic hemostasis techniques, namely electrocoagulation bipolar, hemostatic scalpel ultrasound, and hemostatic suture technique and then checked for AMH, FSH, AFC and PSV levels. On the third day of each menstrual cycle at month 1,3,6, and 12 after laparoscopy where AMH levels were decreased in groups A and B while group C was the same in each cycle, FSH levels increased more in groups A and B than in group C, AFC was increased in Group C compared to Group A and B, whereas PSV was lower in Group A and B than in Group C. From this study it can be concluded that the hemostasis technique in laparoscopy also affects ovarian reserve.<sup>56</sup>

In contrast to research conducted by Jadranka, et al (2014) where 40 reproductive age patients were assessed for ovarian reserve before and 3 months after laparoscopy by assessing ovarian volume with ultrasound other than other markers, there was a decrease in ovarian volume compared to 3 months after laparoscopy, an increase in ovarian volume and ovarian reserve with other markers.<sup>57</sup>

Based on the researcher's analysis, the central theme is how to find an effective laparopy technique by expecting a low recurrence rate while maintaining ovarian reserve. The use of the "stripping of the membrane" technique in this study is very good in removing all cyst pockets, but it can cause the removal of primordial follicles when pulling the pouch in the

Received: December 5<sup>th</sup>, 2019 Accepted: December 28<sup>th</sup>, 2019



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hillus area, thereby reducing ovarian reserves. Avoiding the use of coagulation and using atraumatic forceps can minimize mechanical trauma to the ovaries so as to prevent further reduction of ovarian reserves. In this study, the ovarian reserve was checked before the laparoscopy and after the laparoscopy (the first menstrual cycle after laparoscopy) where 1 month after the procedure, the ovaries had not had time to experience tissue healing (recovery) so this had a very big effect on the results of the assessment of ovarian reserves after laparoscopy, so it is better if ovarian reserve is also checked within 3 and 6 months after treatment after receiving hormonal therapy. In addition, a decrease in ovarian reserve after laparoscopy is also closely related to other supporting factors such as age, BMI, previous cyst surgery history, cyst type, and cyst size. There are many other supporting factors that cause a decrease in ovarian reserve, such as inflammatory factors that can be suggestions for future research.

#### CONCLUSION

Based on the results of the study, it can be concluded that: 1.0varian reserves before the laparoscopic cystectomy were performed, namely AMH levels  $1.77 \pm 0.39$  ng / ml, FSH levels  $6.91 \pm 4.59$  mlU / ml, estradiol levels  $99.65 \pm 77$ , 18 mlU / ml, and 60% of patients with AFC <4. 2. Ovarian reserve after laparoscopic cystectomy, namely AMH levels  $1.54 \pm 0.38$  ng / ml, FSH levels  $10.13 \pm 6.51$  mlU / ml , estradiol levels  $63.67 \pm 35.22$  mlU / ml, and 36% of patients with AFC 7-10. 3. There was an effect of laparoscopic cystectomy on the decrease in ovarian reserve, namely AMH experienced a 13.3% decrease (p = 0.001), FSH experienced a 31.6% increase (p = 0.001), estradiol experienced a 47.8% decrease and a 33% increase (p = 0.001), and the AFC experienced a 47.9% increase (p = 0.003).

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Received: December 5<sup>th</sup>, 2019 Accepted: December 28<sup>th</sup>, 2019



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Ruang Redaksi Andalas Obstetrics and Gynecology Journal, Lantai 3 PPDS Obstetri dan Ginekologi Universitas Andalas, RSUP DR. M. Djamil Padang, Jl. Perintis Kemerdekaan Padang, Sumatera Barat 25127

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