**In The Name of GOD**

**Shiraz University of Medical Sciences**

**School of Medicine**

**Evaluation of the Effect of Size of Endometiroma in the Level of AMH in Women with Endometriesis**

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**Dedicated to:**

**My parents**

**My husband**

**I express my gratitude to my advisors:**

**Prof. Saeed Alborzi**

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Abbreviation:

**AMH**: Anti-Mullerian Hormone

**DIE**: Deep infiltraiting Endometriosis

**DOR**: Diminished on ovarian reserve

**Abstract:**

**Background:** Here we investigated the risk factors for pre-surgical DOR (Diminished ovarian reserve) in Patients with ovarian endometriomas and for DOR after laparoscopic ovarian cystectomy. Endometriosis is a well-known cause of infertility and AMH is an accepted ovarian reserve biomarker. The present study was a retrospective analysis of AMH serum concentration in women with bilateral and unilateral ovarion endometrioma, present of DIE or Not and different size of endometrioma.

**Material and Methods:** this retrospective cross-sectional study include 122 patients age 20-45 years with ovarion endometriomas whom underwent laparoscopic cystectomy from Jul 2014 to Dec 2016 In Dena hospital were retrospectively enrolled and evaluated serum anti-mullerian hormone (AMH) concentration were measured pre-surgically and at 3 and 6 months after surgery.

**Results:** The mean AMH level was 2.2 ng/ml prior to surgery and was reduced to 1.1 at 3 months after surgery, And 1.3 at 6 months after surgery. The pre operative AMH level showed a significant Negative correlation with patient age (r:-0.46). The preoperative AMH level itself was Negatively related to the decline of serum AMH level following surgery. Serum AMH level showed a significant correlation to the it’s stage. But not presence of DIE. Patient with unilateral endometrioma compared with patient with bilateral endometrioma whom underwent laparoscopic ovarian cystectomy had higher initial and 3 and 6 months post-op AMH but it's difference wasn't significant (P>0.05). Mean AMHlevel more reduced 3 and 6 months after surgery in smaller than 3cm size endometrioma compared to greater than 3cm endometrioma but it's difference was not significant (P>0.05).

**Conclusion:** The mean AMH level reduced 3 & 6 month after surgery and in bilateral and smaller than 3 cm size enometriomas, it's decline is higher. The rate of decline in serum AMH level showed a significant correlation to the it's stage & patient's age, but decline in serum AMH showed no correlation with presence of DIE or not.

**Key words:** Anti-Mullerian hormone- cystectomy- Endometrioma- Laparoscopy- cyst diameter.

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# **Chapter 1:**

**Introduction**

# **Background**

Endometriosis means existence glands and endometrial stroma outside the uterine cavity, which is often associated with pelvic pain and infertility (1). Endometriosis involves about 10% of women in childbearing age (2). The severity of endometriosis is defined in degrees 1 to 4 based on its regional involvement: I-IV-American Fertility Society Score (r-AFS) and or the nature and degree of infiltration its lesions (3).

The next ranges from the least to the most sever lesion:

1. SUP: Superficial peritoneal lesion
2. OMA: Endometrioma
3. DIE: Deep Infiltrating Endometrisis

When the lesions penetrate from the peritoneum surface to a depth and spread on the muscular layer of covering organs such as the vagina, bladder, and intestine or ureter (4). Endometrioma is an ovarian cyst that its wall covered by glands and endometrial stroma, which involves between 17-44% of patients with endometriosis (1 and 5). Endometrioma is surrounded by a false capsule sticking to the healthy ovarian tissue. In the creation of endometrioma, two theories are proposed: 1- Ceolomic metaplasia of ovarian epithelium. 2-Cortex invasion inverted after implantation of endometrial spots on the surface of the ovary (5 and 6). Treatment for endometriosis is still under discussion, because endometriosis is most common in women of childbearing age, that the main goal is to maintain fertility power. Therefore, a low-invasive approach with the lowest cost that would restore normal anatomy and reduce pain and prevent recurrence and increase the chances of becoming pregnant should be implemented (1 and 7). Patients with endometriosis with pelvic adhesions do not benefit as well as infertility from drug therapy. Based on the available evidence, removing ovarian cyst by laparoscopy is a preferred method of treatment (8,9,10 and 11). Despite the improvement in the technique and management of symptoms in patients with endometriosis, concerns about the negative effects of surgical treatment on ovarian reserve due to unintentional removal or healthy ovarian tissue destruction adjacent to pseudo capsule endometrioma are growing (12,13 and 14). The ovarian reserve refers to the functional potential of the ovary, which represents the number and quality of the residual primordial follicles at any time interval. There are different tests and markers to assess ovarian reserve. Static tests include age, FSH, LH, E2 (FSH / LH ratio).

 AMH[[1]](#footnote-1), inhibin B, and ultrasound indexes including ovarian volume, antral follicle count and stromal blood flow. Dynamic tests include clomiphene citrate challenge test, exogenous FSH ovarian reserve test, GnRH ogonist stimulation test, (Ovarian stimulation test with GnRH agonist) (15 and 16). AMH is recommended as the most reliable renewable marker (17); due to the during the ovarian cycle its amount stays constant (18-19) and its level is not affected by the use of hormonal drugs (21). When age increases, the amount of AMH reduced (21). AMH is produced by small antral follicles and pre-antral during fertility (21). Similar reports prove that the AMH level predicts the severity of the response to the COS[[2]](#footnote-2) (22 and 23). AMH is a dimetric glycoprotein that is a transforming growth Factor-B family that is produced only by the granulosa cell (GC), which causes calling follicles until they become susceptible to FSH (21 and 24). AMH is strongly dependent on age, which its secretion starts at 36 weekly fetus and at maturity, it reaches its maximum and then begins to decrease continuously and in menopause it reaches an undetectable level (25 and 26). Endometrioma of the ovary may per se reduce the ovarian reserve, removing endometrioma cysts may lead to more damage to ovarian reserve compared with benign ovarian cysts. Age increasing is also a negative factor in ovarian reserve (27). In a study by Simone Ferrero et al, the presence of endometrioma greater than 5 cm during IVF significantly reduced the amount of ovum's obtained during IVF relative to the normal ovary on the other side (28). The level of AMH before surgery itself is inversely related to decreasing AMH after surgery, so the results of this study indicate that preoperative AMH measurements to measure ovarian reserve prior to cystectomy in an older patient are necessary and if the level of AMH is too low, we should consider the risk of postoperative ovarian failure (27). In the current study, AMH has been used as a useful clinical and functional marker for determining ovarian reserve, which was measured before and after laparoscopic endometrium cystectomy, we also examine the impact of age, cyst size, unilateral and bilaterality, as well as existence deep involvement.

# **Chapter 2:**

# **Review of Articles**

Removing ovarian cysts by laparoscopy can reduce the ovarian reserve (29). Concerns exist about damage to healthy ovarian tissue and reduced ovarian reserve (30,31,32).

In a prospective study on the effect of endometrioma removal on AMH in comparison with the control group that did not have ovarian cysts, it was shown that in patients with endometrioma, the level of AMH was lower before operation and after surgical removal of endometrioma AMH levels have fallen further (33). Decreased ovarian reserve after the removal of endometrioma cyst has already been confirmed by a number of articles (33,34,35,36,37,38 and 39).

Although there is a heterogeneity between studies, and includes surgical methods and the duration of follow-up, as well as review method and ovarian reserve test. In 2012, Raffi et al (38) conducted meta-analyzes, including eight prospective studies; The combined analysis of 237 patients with endometrium showed a 38% decrease in AMH after cystectomy. However, only 2 out of 8 studies conducted a follow-up at least 6 months.

Another systemic study by Somigli and et al (40) described 11 studies, 9 of which proved a significant decrease in AMH levels after endometrioma surgery.

Linnea R. Goodman and et al (41) also showed that the level of ovarian reserve decreases significantly one month after cyst removal, and will be some improvement in six months, but it does not return to the initial level.

Uncu et al (33) also in a study that examined ovarian reserve one month and six months after surgery, a similar result to this review were observed.

Alborzi et al (39) also found that the level of AMH decreased by one week, three months and nine months after endometrioma surgery in follow-up of 193 patients undergoing laparoscopic cystectomy.

Three prospective studies that followed up the ovarian reserve about one year after surgery, which Sugita et al. (41) in their study on 39 patients after endometrium cystectomy found that AMH level one year after surgery was similar to its level in one month after surgery.

In 2015, Ding et al. (37) compared the amount of ovarian reserve in 50 endometrioma patients one, six, and twelve months after cystectomy and found that AMH level were significantly reduced in endometrioma patients one month after surgery, but not 6 and 12 months have suggested some improvement in ovarian reserve that in the Linna et al study (41), the similar results were obtained with this study in 6 months, and also in this study found that AMH decreased significantly in people with bilateral endometrioma under cystectomy compared to those with unilateral endometrioma under cystectomy 53% vs. 17%, which has been confirmed in other studies (27, 35, 36, 37 and 42).

Studies have shown different results with a focus on endometrioma size and reduced ovarian reserve.

Studies by Chen et al. (27) found a correlation between the size of endometrioma and the amount of AMH reduction in the month after the operation.

likewise, Celike et al (36) found that the decrease in AMH is more severe and higher six months after surgery when the size of the cyst was greater than 5 cm (65.7% versus 41.3%), in contrast to other studies, there was no relationship between the size of cyst (diameter of cyst) and AMH reduction (35, 43). Damage may occur before surgery, for example, cyst may have devastating effects on the ovarian tissue that surrounds it. Manesch et al (44). Therefore, endometrioma itself may reduce AMH levels.

In a study by Michiokitajima et al. (45), showed that the follicular density in ovarian cortex with endometrioma less than 4 cm is significantly less than the density of the healthy cortex follicles on the opposite side. The size of the cyst may be associated with the time and intensity of inflammatory responses on the endometrioma cortex.

The mechanism that is proposed to reduce ovarian reserve after endometrioma surgery is that the unwanted removal of the healthy ovary tissue is concurrent with ovarian cystectomy and the potential risk of eliminating perfusion residual ovarian tissue due to the effect of the hemostasis during the removal of the ovary (14, 32, 46, and 47).

Therefore, it is likely the cyst that is removed is larger, the larger potential portion of healthy ovarian tissue is removed and more reduction in ovarian reserve occurs. Other studies did not show any relationship between cyst size and AMH reduction (35, 43).

In a study conducted by Rie Ozaki et al (48), showed that age increasing was associated with a diminished on ovarian reserve (DOR[[3]](#footnote-3)) in pre-operative, and the pre-operative serum AMH concentration and bilateral cystectomy were important factors affecting the probability that DOR should occur within one and three months after the operation. It was stated in this study that the amount of ovarian reserve after endometrioma cystectomy depends on the amount of ovarian reserve before surgery.

Several studies (35, 49, 50) have suggested that bilateral removal of ovarian cyst is an important factor that related with reducing the concentration of AMH after endometrioma cystectomy.

In a study by Fateme Mostafaei et al. (51) in Isfahan, it was shown that AMH level decrease after laparoscopy for different types of endometrioma.

Yuh-ming et al also found that patients undergoing bilateral ovary cystectomy significantly decrease the amount of AMH after three months of operation compared with those that undergoing unilateral cystectomy. About 1.4% of patients (144 patients) who participated in their study after removal bilateral cyst suffered a complete loss of ovarian function (ovarian failure) (52).

Wakana Hirokawa et al (35) concluded in their study that reducing ovarian reserve is higher in patients undergoing bilateral ovarian cystectomy due to endometriosis, and in endometrial patients with high Re-ASRM scores. A systematic review carried out by Sanchez and colleagues has shown that endometrioma reduces ovarian reserve but does not depend on its size (45).

In a study conducted by Dorota Nieweglew Ska. (53), it has been shown that there is an inverse relationship between serum level AMH and age patients with endometrioma, and also AMH level in patients with bilateral endometrioma is lower than of control group, but it was not in unilateral endometrioma.

In a study done by Michio Kitajma et al. (45), they observed a significant decrease in AMH in patients after endometrioma cystectomy after 3 months.

In a study by N.K pratap et al. (54) on the comparison of ovarian reserve after cystectomy in endometriomas less than 5 cm in comparison with endometrium larger than 5 cm, it was shown that the smaller cyst and the longer of existence the cyst, damage to the ovaries reserve is greater.

In a study done by Abolfazl Mehdizadeh Kashi (55) and colleagues, showed that laparoscopic cystectomy due to reduce AMH postoperative, especially in patients with bilateral endometrioma, and in endometriomaa with a diameter of at least 5 cm to the top.

In a study by Ji Hyun Jeon et al. (56), it is recommended measurements of preoperative AMH level in endometrioma patients, especially between 30-39 years of age, and bilateral endometrioma and large endometrioses to assessment the prediction of postoperative ovarian reserve reduction, measured.

Yuqing chen et al (27) in a study have shown that ovarian endometrioma may per se reduce ovarian reserve. Endometrioma cystectomy may lead to more damage to ovarian reserve compared with the removal of other benign ovarian cysts. The damage to the ovarian reserve during surgery directly depends on whether endometrioma is bilateral and also the size of the cyst, in particular the size of more than 7 cm, is inversely related to the level of preoperative AMH, and age is a negative factor that effects on ovarian reserve.

In a study conducted by Isabella Streuli et al (57), patients with endometriosis with an ovarian reserve of AMH <1 ng/ml are specifically associated with age, as well as previous endometrioma surgery and as well as bilateral.

A study by Alborzi et al. (39) has shown that patients over the age of 38 have significantly lower AMH levels than patients with age less than 38 years old and also those who have single unilateral cyst, have a significantly higher AMH level than those having multiple bilateral endometriomas and there was no significant difference in postoperative AMH reduction in patients with cysts less than 3 cm and patients who have bilateral cyst had a lower AMH level after surgery and observed a significant reduction in AMH levels after one week, 3 months and nine months after surgery, this has been proven in other studies that followed for 1 month (34 and 50) 3 months (50,58, 59) and 9 months (41).

In other studies, this did not indicate a reduction in AMH level three months after surgery (34 and 60), and by following one month after surgery, indicate by Hirokawa et al (35) and Iwase (49), but not shown by Sugita and Ercan (43).

Sugita (41) has shown that the level of AMH is reduced by one month and one year after surgery, although some patients had more AMH levels one year after surgery than one month before surgery, which suggests that this decrease in AMH with cystectomy may be improved.

The size of the endometrioma was not related with the AMH base level before and after operation in three studies (39, 43, 50).

A meta-analysis reported the deleterious effect of laparoscopic excision of endometrioma on ovarian reserve markers with up to a 40% decrease in serum AMH level (38).

# **Chapter 3:**

# **Materials and Methods**

# **3-1 Study design**

122 patients with endometrioma who underwent laparoscopy and cystectomy in the Dena hospital of Shiraz from July 2014 to December 2016. In this study, the age of patients is between 20-45 years.

Patients have regular menstrual periods that have been hospitalized for surgery due to pelvic and abdominal pain or infertility. Exclusion criteria include:

* Pregnancy
* History of hormonal treatment or taking oral contraceptive pill within three months before surgery
* Existence of ovarian cyst
* Internal diseases and endocrine, such as thyroid disease, hyperprolactinemia, diabetes, PCO
* Suspected or diagnosed ovarian cancer
* The history of surgery on the ovary

And the patients are divided into two groups under the age of 38 and above 38 years.

Before surgery, patients with endometrioma are diagnosed with an experienced specialist (Dr. Saeed Alborzi) with a vaginal sonography or rectal and in terms of unilateral or bilateral, size of cyst, existence of deep involvement and multiplicity and being alone of endometrioma are examined and we measure the relationship of each of the mentioned items with the amount of ovarian reserve.

Surgery is performed by the same physician (Dr. Saeed Alborzi) in the form of laparoscopic cystectomy and the AMH is checked before and three and six months after the operation through a venous sampling by the reference laboratory unit. And the information gathering form is completed by the researcher on the patient file.

The amount obtained analyzes by SPSS software version 21.

# **3-2 Statistical Methods**

Descriptive statistics were presented for qualitative variables in terms of number (percent) and for quantitative variables in terms of mean (Standard Deviation).Independent-Sample T Test, paired t-test, repeated measures ANOVA, U mann-whitney test. One-Way ANOVA, Chi-Square or Fisher exact test and also Pearson Correlation Coefficient were used for inferential statistics. All analyzes were performed in SPSS software version 21 and P-values less than 0.05 was considered significant.

# **Chapter 4:**

# **Results**

Of the 122 participants in this study, 84 (68.9%) were married and 38 (31.1%) were single. The average age of the participants was30.6 $\pm 6∙6$ years and the average duration of the operation was 98$\pm 47∙3$ minutes. Deep involvement was observed in 110 (90.2%) people, 77.8% of participants had only unilateral endometrioma.

The participants baseline characteristics in study are summariesed in table 4-1 & 4-2.

**Table 4-1: Descriptive statistics of qualitative variables under investigation in this research**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Subgroup** | **number** | **Percent** |
| Marital Status | Single | 38 | 31.1 |
|  Married | 84 | 68.9 |
| Age (year) | ≤38 | 107 | 87.7 |
| >38 | 15 | 12.3 |
| Deep Involvement | Yes | 110 | 90.2 |
| No | 12 | 9.8 |
| Stage of endometrioma | 3 | 36 | 29.5 |
| 4 | 86 | 70.5 |
| Size | >5 cm | 70 | 57.4 |
| ≤5 cm | 52 | 42.6 |
| Size | ≤3 cm | 19 | 15 |
| >3 cm | 103 | 85 |
| Child | yes | 40 | 32.7 |
| no | 82 | 67 |
| Location | Unilateral | 95 | 77.8 |
| Bilateral | 27 | 22.2 |

**Table 4-2: Descriptive statistics of quantitative variables under investigation in this research**

|  |  |  |
| --- | --- | --- |
| **Variable** | **Average** | **Standard Deviation** |
| Age | 30.6year | 6.6 |
| Duration of Operation | 98minute | 47.3 |
|  Revised ASRM Score | 59.8 | 32.5 |
| Total endometrioma size | 61.5 mm | 37.2 |
| Initial Amh | 2.2 | 2.1 |
| 3 month  | 1.1 | 1.7 |
| 6 month  | 1.3 | 2.1 |
| Body Mass Index(BMI) | 22.5 | 3.4 |

Repeated measures ANOVA showed that the serum level of AMH decreased significantly 3 month ($p<∙/0001$ ) and 6month ($p<∙/0001$) post-operatively. (table 4-3)

**Table 4-3: Repeated measure ANOVA test for comparing the mean level of AMH before and after Laparascopic Ovarian cystectomy in 122 patients with endometrioma**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **AMH(ng/ml)** | **Per operative** | **3month post-op** | **6month post-op** | **p-value** |
|  | 2.42$\pm $2.47 | 1.06$\pm $1 | 1.1$\pm $1.01 | p$<$0.0001 |

The results of paired t-test for comparing AMH before and after operation was similar. No significant difference in AMH level was seen in 6month post-op compared to 3month after surgery (p=.51 $>$ .05).(table 4-4)

**Table4-4: Paired t-test to compare the initial AMH level, 3 & 6month after surgery in patients with endometrioma**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | Average | Standard deviation | Number | p-value |
| AMH 0 | 2.21 | 2.14 | 122 | $<$.001 |
| AMH 3 | 1.06 | .94 |  |  |
| AMH 0 | 2.42 | 2.47 | 61 | $<$.001 |
| AMH 6 | 1.1 | 1.01 |  |  |
| AMH 3 | 1.06 | 1 | 61 | .511 |
| AMH 6 | 1.1 | 1.01 |  |  |

In this study we compared the role of age, cyst size and bilaterality on the changes of level of AMH after Laparascopic cystectomy.

**Table4-5: Repeated measure ANOVA test for comparing the serum level of AMH before and after Laparascopic ovarian cystectomy in 122 patients with endometrioma in age groups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| variable | Sub group | Pre-operative AMH ng/ml | 3month post-op AMH ng/ml | 6month post-op AMH ng/ml | P-value |
| Age | $\leq $38 yr | 2.63$\pm $2.52 | 1.17$\pm $.99 | 1.19$\pm $1.01 | $<$.001 |
| $>$38 yr | .75$\pm $1.12 | .18$\pm $.41 | .38$\pm $.69 | .079 |

In this study AMH in women more than 38 years had significantly lower baseline level (.75$\pm $1.12 ng/ml) when compared with serum AMH level in women younger than 38 years(2.63$\pm $2.52 ng/ml). (table 4-5).

In this study similar trend to decline in AMH was recorded in those women less than 38 years and older than 38 years. (figure 4-1).



figure 4-1: Comparison the changes in the serum level of AMH before and after Laparascopic ovarian cystectomy in patients with endometrioma in age sub-groups

Independent sample T-test results presented in Table 4-6 showed that the initial, 3-month and 6-month AMH level were significantly different in both groups of women over 38 and less than 38 years old.

**Table 4-6: Independent sample t-test for comparison of AMH in subgroups of age**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Age** | **Average** | **Standard Deviation** | **Number** | **p-value** |
| Amh0 | ≤38 | 2.4 | 2.2 | 107 | 0.003 |
| >38 | 0.7 | 0.8 | 15 |
| Amh3 | ≤38 | 1.2 | 0.9 | 107 | 0.001 |
| >38 | 0.3 | 0.6 | 15 |
| Amh6 | ≤38 | 1.2 | 1.0 | 54 | 0.04 |
| >38 | 0.4 | 0.7 | 7 |

In Table 4-7, Pearson correlation coefficient test results are presented to examine the relationship between quantitative variables. Among the most important findings of this table, there is a positive and significant correlation between the amount of primary AMH and the decreased by 3 and 6 months. This means that whatever amount of primary AMH is greater, the rate of reduction of 3 and 6 months after surgery is also higher. Also, there was no significant correlation between BMI and reduction of 3 and 6 months postoperatively.

**Table 4-7: Results of Pearson Correlation Coefficient test**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Amh0** | **Decreased by 3 months** | **Decreased by 6 months** |
| age | Correlation | -0.46 | 0.32 | 0.39 |
| P-value | <0.001 | <0.001 | 0.002 |
| Amh0 | Correlation | ------- | 0.91 | 0.92 |
| P-value | ------- | <0.001 | <0.001 |
| BMI | Correlation | -0.24 | -0.18 | -0.16 |
| P-value | 0.01 | 0.05 | 0.23 |

In this study repeated measure Anova test showed that there was no significant difference between women with large and small cysts (3cm as a cut off value) regarding the initial level of AMH. (2.49$\pm $2.62ng/ml versus 1.88$\pm $1.06. but it showed that 3 and 6 months post-op AMH level in patient with endometrioma size greater than 3 cm was lower the patient with endometrioma size less than 3 cm (table 4-8).

**Table 4-8: Repeated measure ANOVA test for comparing the serum level of AMH before and after Laparascopic ovarian cystectomy in 122 patients with endometrioma in cyst size groups (cut off value 3cm)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| variable | Sub group | Pre-operative AMH ng/ml | 3month post-op AMH ng/ml | 6month post-op AMH ng/ml | P-value |
| Cyst size | $\leq $3cm | 1.88$\pm $1.06 | .84$\pm $.42 | .92$\pm $.36 | .013 |
| $>$3cm | 2.49$\pm $2.62 | 1.09$\pm $1.06 | 1.13$\pm $1.07 | $<$.001 |

 In the study the trend of decrease in AMH after laparascopic cystectomy was similar between these two study group. (figure 4-2).



figure 4-2: comparing the initial AMH level 3 and 6 months after surgery in endometrial size subgroups (cut off value 3cm)

Independent sample T-test results presented in Table 4-9 showed that the initial, 3-month and 6-month postoperative AMH in patients with endometrium size greater than 3 cm showed no significant difference with the initial, 3-month and 6-month postoperative AMH in patients with less than 3 cm endometrioma.

**Table 4-9: Independent sample t-test for comparing the initial AMH level 3 and 6 months after surgery in endometrial size subgroups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Size** | **Average** | **Standard Deviation** | **Number** | **p-value** |
| Amh0 | ≤3cm | 2.06 | 1.52 | 19 | 0.74 |
| >3cm | 2.37 | 2.24 | 103 |
| Amh3 | ≤3cm | 1.01 | 0.61 | 19 | 0.71 |
| >3cm | 1.07 | 0.98 | 103 |
| Amh6 | ≤3cm | 0.92 | 0.36 | 8 | 0.29 |
| >3cm | 1.28 | 1.07 | 53 |

**Table 4-10: U mann withney test for comparison of mean difference of initial AMH level up to 3month after operation, initial AMH level up to 6month post-op and 3month after surgery up to 6 month post op separation of endometrial size**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Comparative time  | Cyst size group  | Mean difference  | Standard deviation  | Statistic  | p-value |
| Initial AMH up to 3month post- op | $\leq $3cm | 1.05 | 1.19 | 968.5 | .944 |
| $>$3cm | 1.16 | 1.81 |
| Initial AMH up to 6month post- op | $\leq $3cm | .96 | .95 | 197.5 | .757 |
| $>$3cm | 1.37 | 2.17 |
| AMH 3 month post-op up to 6month post-op | $\leq $3cm | -.08 | .26 | 211.5 | .991 |
| $>$3cm | -.036 | .53 |

U mann withney test results presented in table 4-10; showed no difference in mean difference of AMH in sub groups of cyst size in time groups in comparison.

There was no significant difference between women with large and small cysts (5cm as a cut off value) regarding the baseline level of AMH (1.97$\pm $2.15 versus 2.67$\pm $2.63 ng/ml).(table 4-11)

**Table 4-11: Repeated measure ANOVA test for comparing the serum level of AMH before and after Laparascopic ovarian cystectomy in 122 patients with endometrioma in cyst size groups (cut off value 5cm)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| variable | Sub group | Pre-operative AMH ng/ml | 3month post-op AMH ng/ml | 6month post-op AMH ng/ml | P-value |
| Cyst size | $\leq $5cm | 1.97$\pm $2.15 | .83$\pm $.71 | .89$\pm $.84 | .014 |
| $>$5cm | 2.67$\pm $2.63 | 1.19$\pm $1.12 | 1.22$\pm $1.09 | $<$.001 |

Independent sample T-test results, presented in Table 4-12, showed that the initial, 3-month and 6-month AMH levels in patients with endometrium greater than 5 cm had no difference with others.

**Table 4-12: Independent sample T-test for comparing the initial AMH 3 and 6 months after surgery in endometrial size subgroups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Size** | **Average** | **Standard Deviation** | **Number** | **p-value** |
| Amh0 | ≤5 | 2.2 | 2.0 | 52 | 0.94 |
| >5 | 2.2 | 2.2 | 70 |
| Amh3 | ≤5 | 1.1 | 0.8 | 52 | 0.93 |
| >5 | 1.1 | 1.0 | 70 |
| Amh6 | ≤5 | 0.9 | 0.8 | 22 | 0.22 |
| >5 | 1.2 | 1.1 | 39 |

In this study there was 95 women (77.8%) with unilateral and 27 patients (22%) with bilateral endometrioma. The baseline AMH was 2.48$\pm $2.75 in unilateral endometriomas versus 2.26$\pm $ 1.6 in bilateral endometriomas. Repeated measure ANOVA showed that the serum level of mean AMH changes in both subgroup of unilateral (p$<$.001) and bilateral (p$<$.001) endometrioma was meaningful. (table 4-13)

**Table 4-13: Repeated measure ANOVA test for comparing the serum level of AMH before and after Laparascopic ovarian cystectomy in 122 patients with endometrioma in bilaterality groups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| variable | Sub group | Pre-operative AMH ng/ml | 3month post-op AMH ng/ml | 6month post-op AMH ng/ml | P-value |
| Bilaterality | Unilateral | 2.48$\pm $2.75 | 1.12$\pm $1.01 | 1.13$\pm $1.01 | $<$.001 |
| Bilateral | 2.26$\pm $1.6 | .89$\pm $.97 | 1.02$\pm $1.30 | $<$.001 |

Repeated measure Anova showed that patient with unilateral endometrioma whom underwent operation had higher level of initial AMH compared with patient with bilateral endometrioma which it remained higher at the end of follow- up period (table 4-13) but U mann withney test and One way Anova test showed that it's difference was not significant. (P>0.05) (table 4-14 , table 415).

**Table 4-14: One-way ANOVA test to compare the initial AMH level 3 and 6 months after surgery in endometrium-type subgroups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Type of endometrium** | **Average** | **Standard Deviation** | **Number** | **p-value** |
| Amh0 | unilateral | 2.27 | 2.28 | 95 | 0.59 |
| bilateral | 2.01 | 1.56 | 27 |
| Amh3 | unilateral | 1.12 | 0.94 | 95 | 0.21 |
| bilateral | 0.87 | 0.90 | 27 |
| Amh6 | unilateral | 1.13 | 1.01 | 44 | 0.71 |
| bilateral | 1.02 | 1.03 | 17 |

**Table 4-15: U mann withney test for comparison of mean difference of initial AMH level up to 3month after operation, initial AMH level up to 6month post-op and 3month after surgery up to 6month post op separation of endometrial bilaterality**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Comparative time**  | **Bilaterality sub group**  | **Mean difference**  | **Standard deviation**  | **Statistic**  | **p-value** |
| Initial AMH up to 3month post- op | Unilateral | 1.14 | 1.85 | 1139.5 | .378 |
| Bilateral | 1.15 | 1.15 |
| Initial AMH up to 6month post- op | Unilateral | 1.35 | 2.32 | 322 | .403 |
| Bilateral | 1.24 | 1.16 |
| AMH 3 month post-op up to 6month post-op | Unilateral | -.006 | .52 | 337 | .551 |
| Bilateral | -.14 | .45 |

The pattern of AMH changes was comparable between these to study group. (figure 4-3)



figure 4-3: The pattern of AMH changes between patients with unilateral and bilateral endometrioma

Of the 122 participants in this study 86 (70.5%) were in stage 4 endometriosis and 36 (29.5%) was in stage 3.(table 4-1)

Repeated measure ANOVA showed that level of AMH decreased significantly 3month and 6 month post operatively in both groups(stage 3 p= .002) (stage 4 p$<$.001). (table 4-16) with similar trend of decline in AMH level in both subgroups. (diagrame 4-4)

**Table 4-16: Repeated measure ANOVA test for comparing the serum level of AMH before and after Laparascopic ovarian cystectomy in 122 patients with endometrioma in stage groups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| variable | Sub group | Pre-operative AMH ng/ml | 3month post-op AMH ng/ml | 6month post-op AMH ng/ml | P-value |
| Stage of endometriosis | 3 | 2.58$\pm $1.61 | 1.56$\pm $.86 | 1.62$\pm $1.09 | .002 |
| 4 | 2.35$\pm $2.75 | .86$\pm $.99 | .89$\pm $.91 | $<$.001 |



figure 4-4: comparison of AMH changes during 6month post- op in patients with endometrioma at different stage

Independent sample T-test results, as presented in Table 4-17, showed no differences in the initial AMH level in patients with Stage 3 and 4, but the AMH level in 3 months and 6 months after operation was significantly lower in Stage 4 patients than in Stage 3 patients, that suggesting much more reduction AMH in patients with higher staging.

**Table 4-17: Independent sample T-test for comparison of initial AMH level 3 and 6 months after surgery at different stages**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Stage** | **Average** | **Standard Deviation** | Number | **p-value** |
| Amh0 | 3 | 2.5 | 1.9 | 36 | 0.37 |
| 4 | 2.1 | 2.2 | 86 |
| Amh3 | 3 | 1.6 | 0.9 | 36 | <0.001 |
| 4 | 0.8 | 0.9 | 86 |
| Amh6 | 3 | 1.6 | 1.1 | 17 | 0.01 |
| 4 | 0.9 | 0.9 | 44 |

Independent sample T-test, as presented in Table 4-18, showed a significant difference in initial, 3-month and 6-month AMH in patients with and without children.

**Table 4-18: An independent sample t-test for comparison of AMH in subgroups with and without child**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Child** | **Average** | **Standard Deviation** | **Number** | **p-value** |
| Amh0 | with | 2.6 | 2.3 | 82 | 0.003 |
| without | 1.4 | 1.3 | 40 |
| Amh3 | with | 1.3 | 1.0 | 82 | 0.001 |
| without | 0.7 | 0.7 | 40 |
| Amh6 | with | 1.3 | 1.0 | 42 | 0.03 |
| without | 0.7 | 0.7 | 19 |

The results of this study showed that there was a significant difference between initial AMH, three months and six months after operation in patients with and without gravid, meaning that the initial AMH level, three months after surgery and six months after surgery, in women with child it was lower than women without child. (figure 4-5)



figure 4-5: Comparison of AMH in patients with and without child according to initial amount 3 and 6 months after surgery

**Table 4-19: An independent simple t-test for comparison of AMH in subgroups with and without children with age**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Child** | **Age** | **Standard deviation** | **number** | **p-value** |
| AMH | with | 34.4 | 5.14 | 40 | $<$.001 |
| without | 28.58 | 6.35 | 82 |

An independent simple t-test showed that mean age of patients without child was significantly less than patients with child. (p$<$.001)(table 4-19)

**Table 4-20: Independent sample T-test for comparison of initial AMH level, 3 and 6 months after surgery in endometrial patients with and without DIE**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Deep involvement** | **Average** | **Standard Deviation** | **Number** | **p-value** |
| Amh0 | No | 2 | 1.6 | 12 | 0.70 |
| Yes | 2.2 | 2.2 | 110 |
| Amh3 | No | 0.9 | 0.9 | 12 | 0.48 |
| Yes | 1.1 | 0.9 | 110 |
| Amh6 | No | 0.5 | 0.8 | 5 | 0.15 |
| Yes | 1.2 | 1 | 56 |

Independent sample T-test showed that there was no discrepancy between the initial, 3-month and 6-month AMH level in people with and without deep involvement (Table 4-20).

The correlation between the operating time and the 3-month reduction was 0.04 and its p-value was 0.66, which was not significant.

The correlation between the operating time and the 6-month reduction was 0.09 and its p-value was 0.49, which was not significant.

# **Chapter 5:**

# **Discussion and Conclusion**

According to the available evidence, the removal of ovarian cysts by laparoscopy is considered the preferred method of treatment for endometriosis (8, 9,10 and 11). Despite the improvement in the technique and management of symptoms in patients with endometrioma, concerns about the negative effects of surgical treatment on ovarian reserve are growing due to the unintentional removal or damage to the healthy ovarian tissue adjacent to pseudo capsule of endometrioma (12,13,14). In this study we concluded that AMH level statistically decreases in endometrioma patients three and six months after cystectomy surgery. This study showed that the level of initial, 3-months, and 6-months post-op AMH, in those with and without deep involvement were not different together (Table 4-15). Decreased ovarian reserve after the removal of the endometriomal cyst has already been confirmed by a number of articles (33, 34, 35, 36, 37, 38,39), which is consistent with our study outcomes. Another systematic review by Somigli and et al. (40) described eleven studies, of which 9 proved a significant reduction in AMH level after endometrioma surgery. The mechanism for reducing ovarian reserve after endometrioma surgery is that the unwanted removal of the healthy ovarian tissue is simultaneous with ovarian cystectomy and also the potential risk of eliminating perfusion residual ovarian tissue due to the effect of the hemostasis during the removal of the ovary (14, 32, 46, 47). In a study done by Michio kitajma et al. (45), they observed a significant reduction in AMH in patients after endometrioma cystectomy after three months. The results of this study showed that there was no significant difference between the amount of initial AMH level in patients with endometrioma size less than or equal to 3 cm and greater than 3 cm. The results of this study showed that the, three month and six months postoperative AMH level in patients with endometrioma size greater than 3 cm was more than patients with endometrioma size less than 3 cm. but this difference wasn't significant because of number of paticipants in our study (P>0.05) that we can explaine this difference by the greater technical difficulty in stripping smaller endomerioma cysts, which induces bigger ovarian tissue damaged and more ovarian follicular loss, in addition to vascular compromise and inflammation (39). Likewise, Celice et al (36) found that decrease AMH level six months after the surgery, when the cyst is more than five centimeters, is more intense and more. In contrast in other studies, there was no relationship between the size of cyst (diameter of cyst) and the decrease AMH level (35,43). Study of Hirokawa et al and study of urcan et al and other studies (39,45,50). In a study by Nk pratap et al. (54) on comparison of ovarian reserve after cystectomy in endometriomas less than 5 centimeters in comparison with endometrioma larger than 5 cm, it was shown that whatever the cyst is smaller, damage to the ovarian reserve is greater. In a study done by Abolfazl Mehdizadeh Kashi (55) and colleagues, it was shown that, laparoscopic cystectomy reduces postoperative AMH, especially in patients with endometrioma with a diameter of at least 5 cm to up. A systematic review carried out by Sanchez et al. has shown that endometrioma reduces ovarian reserve, but this reduction does not depend on its size (45). Yugingchen et al. (27) in a study have shown that ovarian endometrioma may reduce the ovarian reserve by itself, endometrioma cystectomy may cause further damage to the ovarian reserve. Damage to ovarian reserve during surgery, it is directly related to whether endometrioma is bilateral and the size of the cyst, in particular the size above 7 cm, has an inverse relationship with the level of preoperative AMH. Age is also a negative factor that affects ovarian reserve. The results of this study showed that the comparison of the pre-operative AMH and the three and six months postoperative confirmed the significant decrease in AMH three and six months after the operation compared to the initial AMH, witch the difference between the six months and the three months was not significant. The results of the study showed that the initial AMH level in patients with Stage 3 and 4 had no difference, but AMH level in the 3 and 6 months after operation were significantly lower in Stage 4 patients than Stage 3 patients, which indicates a much higher drop AMH in patients with higher staging. In this study, results showed that patients with unilateral endomerioma whom underwent operation had higher level of initial AMH compared with patient with bilateral endometrioma which remained higher at the end of the follow–up period, but it's difference was not significant (P>0.05). In other studies, this has been proven (27,32,36,37,41,42). Several studies have suggested that the removal of bilateral ovarian cyst is an important factor, which is associated with a decrease in AMH concentration after endometrioma cystectomy (35,49,50). In the study of Ric Ozaki et al. (48), it was also shown that the amount of ovarian reserve loss is related to bilateral cystectomy. Yuh-ming et al. Also found that patients undergoing bilateral ovarian cystectomy were significantly to have less AMH level after three months compared to those undergoing unilateral ovarian cystectomy (52). Wakana Hirokawa et al. (35) concluded in their study that reducing ovarian reserve in patients undergoing bilateral cystectomy due to endometriosis is higher. In a study by Abolfazl Mehdizadeh Kashi (55) and colleagues, it has been shown that laparoscopic cystectomy reduces postoperative AMH, especially in patients with bilateral endometrioma involvement. Table 4-7 indicates a positive and significant correlation between the initial AMH and the 3-month and 6-month reductions; it means that whatever the initial AMH level is more, decreased AMH level three and six months after surgery is also more. Also, in this study, an inverse correlation was found between the increase in age and the initial AMH (-0.46), meaning that as the age increases, the initial AMH decreases, but the reduction rate in 3 and 6 months increases. This issue was confirmed in a study by Yuging Chen et al. (27). In this study, the level of AMH before surgery itself have a reverse correlation with decreasing AMH after surgery. Yuging chen et al, implicitly indicate that preoperative AMH measurements are necessary to measure ovarian reserve prior to cystectomy in older patients, and if the level of AMH is too low, then the risk of postoperative ovarian failure should be considered. Also, in our study, there was no significant correlation between BMI and reduction of AMH three and six months after surgery. In a study conducted by Rie Ozaki et al. (48), has shown that increasing age were associated with reduced ovarian reserve before and after surgery and the concentration of pre-operative serum AMH affects the probability of decreasing ovarian reserve one and three months after surgery. In a study done by Dorota Nieweglew Ska et al. (53), showed that there is a reverse relationship between the serum AMH level and the age of the endometrioma patient. The results of this study showed that there was a significant difference between initial AMH, three months and six months after operation in patients with and without child, meaning that the initial AMH level, three months after surgery and six months after surgery, in women with a child it was lower than women without child. The results of this study showed that the initial AMH level, three months after surgery and 6 months after surgery, in women over 38 years of age less than women under the age of 38 years. A study by Alborzi et al. (39) has shown that patients over the age of 38 have significantly lower AMH level than patients with age less than 38 years old. As well as those who have single unilateral cyst, have significantly higher level of AMH than those who have bilateral multiple endometriomas cyst, and patients with bilateral cyst had a lower postoperative AMH level. And also significantly decreased in AMH level after one week, three months and nine months after surgery were observed, which this has been proven in other studies that have one-month follow-up (34 and 50) three months' follow-up (50,58,59) and nine months' follow-up (41). The operation time did not correlate with a decrease of 3 and 6 months after the AMH operation. There was no relationship between BMI and AMH reduction.

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**خلاصه:**

**مقدمه:** در این مطالعه ما ریسک فاکتورهایی که باعث کاهش ذخیره ی تخمدان قبل و بعد از عمل لاپارسکوپیک سیستکتومی می شوند را بررسی می کنیم. اندمتریوز به عنوان یکی از علل نازایی به خوبی شناخته شده است و AMH یک بیومارکر مورد قبول جهت ارزیابی ذخیره تخمدان می باشد. این مطالعه یک مطالعه ی مقطعی گذشته نگر می باشد که غلظت سرمی AMH را در خانم های با اندومتریومای یک طرفه و دو طرفه ، با اندومتریومای عمقی (DIE) و نیز سایزهای متفاوت اندومتریوما را آنالیز می کند.

**روش کار:** این مطالعه، مطالعه ای مقطعی و گذشته نگر است که تعداد 122 بیمار اندومتریومایی درسنین 45-20 سال را که تحت لاپاراسکوپیک سیستکتومی در بیمارستان دنا قرار گرفته را از تیر 1393 تا آذر 1395 با AMH اولیه و سه و شش ماه بعد از عمل بررسی میکند.

**نتایج:** میانگین AMH اولیه ng/ml2/2 بوده است. کاهش سه ماهه AMH ng/ml 1/1 و کاهش شش ماهه ng/ml 3/1 بوده است. هر چه سن بیمار بالاتر باشد سطح AMH اولیه پایین تر است ( همبستگی 46/0-) میزان AMH بعد از عمل در بیماران با استیج بالاتر کمتر بود. (pvalue 0<001) و میزان کاهش AMH بعد از عمل رابطه ای به وجود یا عدم وجود DIE نداشت و هر چه AMH اولیه بیشتر باشد، کاهش سه ماهه و شش ماهه AMH بیشتر است(pvalue <0.001) در بیماران دارای اندومتریومای کوچکتر از cm3 در مقایسه با بیماران دارای اندومتریومای بزرگتر از cm3 میزان کاهش AMH سه و شش ماه بعد از عمل بیشتر بود ولی از لحاظ آماری به علت کمی تعداد نمونه این اختلاف معنی دار نبود. و نیز در بیماران دارای اندومتریومای دو طرفه میزان کاهش AMH 3 و 6 ماهه بعد از عمل بیشتر بود. ولی از لحاظ آماری این کاهش معنی دار نبود.

**بحث و نتیجه گیری:** غلظت AMH قبل از عمل و استیج اندومتریوما و اندازه اندومتریوما فاکتورهای مهمی هستند که میزان ریسک کاهش AMH بعد از عمل را پیش بینی می کند و هر چه سن افزایش یابد، AMH اولیه کاهش می یابد و با افزایش سن میزان کاهش 3 و 6 ماهه AMH افزایش می یابد. و هرچه اندازه کیست کوچکتر از cm3 باشد آسیب وارده به ذخیره تخمدان بعد از عمل بیشتر می شود.

**کلید واژه:** آنتی مولرین هورمون – لاپارسکوپیک سیستکتومی – اندومتریوما- قطر کیست.

**دانشگاه علوم پزشکی شیراز**

**دانشکده پزشکی**

عنوان:

**بررسی تاثیر سایز اندومتریوما بر میزان AMH در خانم های مبتلا به اندومتریوز**

توسط:

**فاطمه عسکری**

پایان نامه ارائه شده به دانشکده پزشکی به عنوان بخشی از فعالیت های لازم برای اخذ درجه دکترای تخصصی در رشته زنان و زایمان

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1. Anti mulerian hormone [↑](#footnote-ref-1)
2. Controlled Ovarian Stimulation [↑](#footnote-ref-2)
3. Diminished on ovarian reserve [↑](#footnote-ref-3)