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The Impact of Endometrioma Treatment on Ovarian Reserve

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Objectives: To evaluate the ovarian reserve by measuring AMH level after the both treatment of drug and surgery for Endometrioma. **Methods:** We studied 129 patients who have diagnosed with ovarian endometrioma, aged 20-46 years, using case-control study design. There are 4 groups with medication and surgeries. **Results:** There were significant reduction of pain in patients who received synthetic progestin ($p = 0.001$) groups. Serum AMH were 3.48 ± 0.9 before treatment and 3.41 ± 1.0 after treatment respectively ($p = 0.456$). Prior treatment of laparoscopic surgery with progestin 3 months, it decreases abdominal lower pain ($p = 0.001$) and dysmenorrhea ($p = 0.001$). Serum AMH level were 3.11 ± 1.8 before surgery and 2.21 ± 0.2 after surgery, respectively ($p = 0.005$). **Conclusions:** Laparoscopic surgery might be decrease ovarian reserve which leads to infertility later life in women who has ovarian endometrioma with ovarian cystectomy.

Keywords: Ovarian Endometrioma, Laparoscopic Surgery, Infertility, Synthetic Progestin, Antral Follicle

Introduction

Endometriosis is defined by the presence of tissue similar to uterine endometrium located outside the uterus in places physiologically inappropriate [1]. Endometriosis is usually located in the pelvic cavity and is most commonly detected on the ovaries, where it is called endometrioma. When endometrioma occur, they are identified as dark fluid-filled cavities or "chocolate cysts" [2]. The cause of endometriosis is unknown. However, there are few common theories, including ectopic metaplasia of ovarian cyst, transfer of endometrial tissue with functional cysts, and menstrual debris backflowing into the pelvic and abdominal cavity [3]. Endometriosis is a chronic, relapsing disorder, which causes chronic pelvic pain, lower abdominal pain, painful sexual intercourse and infertility [4].

Endometriosis associated infertility is explained by 1) menstrual cycle hormones that may induce inflammation in endometriosis tissue and resulting in its adhesion in the fallopian tube, which causes tubal factor infertility, 2) ovarian cyst enlargement that increases ovarian tissue inflammation and causes a reduction of the number of growing follicles at different stages of maturation (ovarian reserve) [5].

Management of endometrioma is still debatable. However, each patient's symptoms, age, desire to conceive, risk of malignancy, ovarian reserve before treatment, treatment before surgery and characteristic of the cyst (size, location, adhesion, etc.) needs to be considered [6]. There are several treatment methods, including suction (along with ultrasound or laparoscopy), drainage, electrocoagulation, ablation by laser and cutting the cyst [2, 7].

The CA 125 marker test is a marker for ovarian, endometrial, peritoneal and fallopian tube cancers and must be done if an ultrasound or clinical signs identify enlarged ovaries and detects any cysts [7-9]. Its normal range is 0 – 35 units/ml and the level of the marker is also increased in patients with endometriosis.

The incidence of endometriosis has been increasing. In worldwide, 1 in 10 reproductive age of women have endometriosis. A total of 5.5 and 16 million women has endometriosis in the USA and Europe. Approximately 176 million women ages 19-45 are victims of this disease globally [10]. Strikingly, 60-80% of female infertility is caused by endometriosis [5, 11].

Several studies have investigated endometriosis treatment options and their results. The Reproductive Care Center of USA studied the result of synthetic progestin before and after laparoscopic surgery and evaluated the recurrence rate [2, 12-20]. Muzii et al. studied the histological features of endometriosis and revealed that secondary inflammation initiated endometriosis and that inflammatory fibrosis a key characteristic of this disease [2, 18]. The Japanese scientist O.Yoshiaki and his team studied synthetic progestin dienogest's effect on endometrioma recurrence [21]. Yoshiaki and other researchers showed that diegonest could prevent recurrence, infertility, help preserve ovarian reserve [21-24], and improve symptoms [25, 26].

In recent years, scientists have reported that serum anti-müllerian hormone (AMH) is a significant marker to define ovarian reserve, which correlates the number of ovarian antral follicles [27,28]. AMH is a glycoprotein hormone that is released from ovarian follicles. A decreased number of follicles results in a reduction of AMH [29]. The level of AMH decreases with age [30]. Normally, the level of AMH fluctuates between 2.0 – 12.0 ng/ml, within this reference range [31, 32].

In 2006, Andersen and Byskow reported that estradiol and anti-müllerian hormones released from ovaries' small follicles correlated with steroid hormone released from granulosa cells [33]. As the number of ovarian follicles decreases, the level of estradiol decreases and which increases the follicle stimulating hormone (FSH) levels. The anterior pituitary gland secretes FSH, and it initiates follicular growth. Elevated FSH level indicates poor ovarian function [34]. Lower levels of AMH (< 0.5 ng/ml) predict diminished ovarian reserve. Therefore, women over the age of 35 who are planning to conceive need to have ovarian reserve tests [35]. AMH levels are suggested to estimate a woman's reproductive age [32, 36]. Furthermore, many researchers have suggested using AMH levels to diagnose infertility related to endometriosis [27].

Several studies evaluated the recurrence of endometriosis after using progestin treatment. For instance, Liang et al. studied efficacy, safety and recurrence after using progestin. Their study showed progestins are effective for endometriosis through increasing apoptosis and adhesion and decreasing proliferation [37]. Moreover, the Japanese scientists Tanaguchi et al. studied the efficacy of progestin treatment for endometriomas. They found that the progestin-only injectable contraceptive norethisterone enanthate (NET-EN) reduces the size of ovarian endometrioma [38].

In this study, we aimed to evaluate the ovarian reserve by measuring AMH levels after both treatment with drugs (synthetic progestin or non-steroidal anti-inflammatory drug) and surgery for endometrioma. Moreover, we compared the CA-125 marker levels during drug and surgical treatment. Our study's novelty is that we compared the ovarian reserve of groups of patients who received and did not receive progestin treatment before the surgery.

Materials and Methods

Study design and sampling

This was a prospective hospital-based case-control study of 129 women, ages 20-46, diagnosed with ovarian endometriosis at the National Center for Maternal and Child Health in Ulaanbaatar, Mongolia, between 2018 and 2019. All women were seen by obstetricians/gynecologists, and 117 of them completed a specific questionnaire. Before the treatment, AMH and CA-125 were measured in 5 ml blood taken the 2 - 3rd day of their menstrual cycle using a Cobas E411 Analyzer immunoassay apparatus (Hitachi, Japan). The CA-125 measurements between 0 - 35 unit/ml and AMH measurements between 2.0 - 12.0 ng/ml were the normal ranges. Transvaginal ultrasonography (NeuEcho-10, 7.5 MHz Neusoft Medical Systems, China) was performed between the 3-5th day of the menstrual cycle. The International Federation of Gynecology and Obstetrics (FIGO) 5B and 5M international classification was used to determine the Endometrioma's stage [43] and include 4 stages: minimal (1 - 5 score) and mild (6 - 15 score), moderate (16 - 40), and severe (> 40).

The decision regarding the type of treatment was based on the physicians' recommendation. Patients with minimal and mild endomitosis were typically treated with synthetic progesterone (dienogest) or a nonsteroidal anti-inflammatory drug (ibuprofen). When prescribed, dienogest 2 mg orally daily was started after 3 - 5 days of menses and was taken for 28 days, and ibuprofen 400 mg orally every 12 hours was started on day 1 of menses and was taken for 5 days. Patients with minimal and mild stages who failed 3 ~ 6 months of nonoperative treatment and those with moderate and severe endometriosis underwent laparoscopic excision. The patients were stratified into the following groups: Group I received only oral dienogest, Group II received only oral ibuprofen, Group III received dienogest for 3 months after surgery, and Group IV dienogest for 2 months before surgery.

After obtaining informed consent, laparoscopy was performed. All laparoscopic cystectomy operation was performed under the general anesthesia between the 5 - 9th day of the patient's menstrual cycle, using routine laparoscopic equipment (Olympus, Japan). The endometriosis stage was defined according to the American Society of Reproductive Medicine's guidelines, using 2 extra trocars [39].

Mild endometriosis was removed by electrocoagulation. Endometriomas larger than 4 cm were carefully removed with the cyst wall. Hemostasis was achieved with atraumatic forceps and bipolar forceps electrocoagulation. All endometrioma removed during the surgery were sent for pathologic analysis.

Inclusion criteria

Women were included in the study if they were diagnosed with endometriosis as proven by signs, symptoms, examination, lab finding, ultrasonography and provided informed consent.

Exclusion criteria

Women were excluded from the study if they 1) chose not to obtain the labs or ultrasound exam, 2) had any cancer signs detected by the international classification [44], 3) had a drug allergy, 4) contraindication to receiving luteinizing hormone, 5) had a endocrinology disorder, 6) had history of chemo and radiation therapy, 6) acute inflammation in pelvic cavity, 7) had ovarian cyst which is not caused by endometriosis, and 8) infertility not caused by endometriosis.

Statistical analysis

Chi-square test was used for the compare frequencies between two different treatment groups. The paired t-test was used to compare the variables between before and after treatment. Multiple logistic regression was performed to identify the risk factors for abnormal anti-müllerian hormone levels. Statistical analysis were performed using Excel and SPSS-20.0 version. A p-value of < 0.05 was considered statistically significant.

Ethical statement

The study protocol (№2018/3-06) was approved by the Research Ethics Committee at Mongolian National University of Medical Sciences in 23rd Feb 2018. All participants were informed about the study and provided written informed consent.

Results

One hundred twenty-nine women between 20 and 46 years of age participated in the study, and their average age was 31.6 ± 6.8 years. The majority of participants were between 25 and 29 years old. The average age of their first period was 14.1 ± 1.2 years (Table 1). One hundred fourteen (88.4%) of participants had regular menstrual cycles and 15 (11.6%) had an irregular menstrual cycle. Ninety-four (72.9%) of the participants were seen for non- obstetrical problems, 18 (14.0%) had a history of abortion, 7 (5.4%) had had a miscarriage, 3(2.3%) had a history of spontaneous abortion, 1 (0.8%) had had a preterm birth and 6 (4.7%) had other problems (Table 2). The AML level was below normal in 35 women between the ages of 20 - 35 (Table 4).

Table 1. Socio-demographic characteristics of the participants (n = 129)

Variables	**Mean ± SD**	
Average age	31.6 ± 6.8 years	
Age by group (years)	N	%
20 - 24	16	12.4
25 - 29	46	35.7
30 - 34	27	20.9
35 - 39	14	10.9
> 40	22	17.1
Ethnicity		
Khalkh	117	90.7
Kazak	8	6.2
Others	4	3.1
Residence		
Urban	74	63.4
Rural	55	42.6
Marital status		
Married	89	69.0
Partner	9	7.0
Single	31	24.0
Working condition		
Normal	121	93.8
Average	5	3.8
Toxic	3	2.4
Occupation		
Hunting	4	3.1
Manufacture, construction	12	9.3
Hand craft, light industry	7	5.4
Machine, mechanism	7	5.4
Health care, education	51	39.5
Trade and service	28	21.7
Armed forces	3	2.3
Vocational training	5	3.9
Other	12	9.3
Educational status		
Tertiary	108	83.7
High school	11	8.3
Middle school	5	3.8
Elementary school	3	2.3
None	2	1.5
Unhealthy habits		
Alcohol	3	2.3
Smoke	7	5.3
None	119	92.2

Data reported as mean ± standard deviation, or n (%)

Table 2. Reproductive history of the participants (n = 129)

Variables	Mean ± SD	
Duration of menstrual cycle (days)	27.9 ± 3.5	
Average menses duration (days)	4.2 ± 1.3	
Average amount of blood (ml)	107.5	
Age of first period (years)	**N**	**(%)**
10 - 15	111	86.0
16 - 19	18	14.0
Menstrual cycle		
Regular	114	88.4
Irregular	15	11.6
Number of pregnancies		
0	67	51.9
1	25	19.4
2	18	14.0
3	8	6.2
4	3	2.3
5	6	4.7
6	2	1.6
Obstetric problems		
Normal	94	72.9
Abortion	18	14.0
Spontaneous abortion	3	2.3
Miscarriage	7	5.4
Premature birth	1	0.8
Other	6	4.7
Number of live births		
0	75	58.1
1	30	23.3
2	16	12.4
3	5	3.9
4	2	1.6
5	1	0.8
Contraception		
Yes	18	14.0
No	111	86.0
Sexually Transmitted Disease		
Yes	4	3.8
No	125	96.9
Syphilis	2	1.5
Gonorrhea	1	0.8
Trichomoniasis	1	0.8

Data reported as mean ± standard deviation, or n (%)

Table 3. General characteristics of women who were diagnosed endometriosis (n = 129)

Variables	Mean ± SD	
Body weight (kg)	60.6 ± 9.8	
Height (cm)	159.3 ± 18.6	
BMI	N	%
< 18.5	6	4.7
18.5 - 24.9	103	79.8
25.0 - 29.9	18	14.0
30.0 - 34.9	2	1.6
General health		
Mild	8	6.2
Moderate	120	93.0

Severe	1	0.8
Abdominal tenderness		
Yes	118	91.5
No	11	8.5
Intensity of tenderness		
Mild	25	19.4
Moderate	60	46.5
Severe	33	25.6
Peritoneal reaction		
Yes	72	55.8
No	57	44.2
Intensity of peritoneal reaction		
Mild	44	34.1
Moderate	22	17.1
Severe	6	4.7
Multiple spots on cervix and vagina		
Yes	7	5.4
No	122	94.6

Data reported as mean ± standard deviation, or n (%)

Table 4. Anti-müllerian hormone levels by age group (n = 129)

	Anti-Müllerian Hormone		
	Normal levels (ng/ml)	Abnormal (n=48)	Normal (n=81)
Age groups (years)		N (%)	N (%)
20 - 24	3.55-4.33	9 (18)	11 (13)
25 - 29	3.03-3.87	20 (42)	24 (29)
30 - 34	2.34-3.55	12 (25)	17 (21)
35 - 39	1.78-3.24	4 (8.0)	9 (11)
≥ 40	0.73-2.13	3 (7.0)	20 (25)

The participants' average AMH level decreased but not significantly following laparoscopic surgery (2.7 ± 1.6 vs 2.3 ± 1.6, p = .010, n = 63). In 18 cases, the AMH level was < 2 ng/ml, and in 43 cases, it measured more > 2 ng/ml after the 3 months of non-operative treatment. In 52 cases, > 2 antral follicles were identified. One month after the laparoscopic surgery, the AMH level was under 2 ng/ml and endometrioma was detected in both ovaries in 27 cases. Moreover, the number of antral follicles counted was less than 2 in 52 cases, indicating the number of antral follicles decreased after the laparoscopic surgery (Table 5). Compared to preoperatively, the AMH levels dropped significantly after the surgery for severe endometriosis (2.3 ± 1.8 vs. 1.68 ± 0.2 ng/ml, p = 0.000, n = 31). The number of antral follicles number and AMH levels was higher in Group I or women who received dienogest than in women who received laparoscopic surgery. Also, there was no risk to the ovarian reserve in Group I. The ovarian reserve measured higher in women who received dienogest before and after the surgery (p < 0.050).

Table 5. Comparison anti-müllerian hormone levels and antral follicle numbers and treatment received. (n = 129)

	Treatment Groups		
Variables	Conservative	Laparoscopy	[a]p-value
Anti-müllerian hormone	N (%)	N (%)	
< 1.9 ng/ml	19 (16.1)	27 (22.7)	0.050*
≥ 2.0 ng/ml	45 (36.1)	38 (26.1)	
Antral follicle numbers			
< 2	11 (8.5)	52 (40.3)	0.001*
≥ 2	52 (40.3)	14 (10.9)	

[a]using Pearson's Chi-square test, *p < 0.05

The AMH did not significantly decrease after receiving synthetic progestin (3.48 ± 0. vs 3.41 ± 1.0 ng/ml, p = 0.450, n=42). The AMH also did not significantly drop after receiving ibuprofen (3.68 ± 0.8 vs.3.11 ± 0.8 ng/ml, p = 0.210, n = 21).

Table 6. Anti-müllerian hormone values before and after treatment (n = 129)

	Anti-Müllerian Hormone		
	Before (ng/ml)	After (ng/ml)	[a]p-value
Treatment methods (n = 129)	Mean ± SD	Mean ± SD	
Total treatment (n = 63)	2.88 ± 1.3	2.64 ± 1.45	0.519
Group I (dienogest) (n = 42)	3.48 ± 0.9	3.41 ± 1.0	0.456
NSAID (n = 21)	3.68 ± 0.8	3.11 ± 0.8	0.212
Laparoscopy			
Total surgery (n = 66)	2.69 ± 1.8	1.95 ± 1.1	0.012*
Moderate and severe endometrioma laparoscopy soon after clinical and US diagnosis (n = 35)	2.3 ± 1.8	1.68 ± 0.2	0.007*
Unilateral ovarian cyst	2.14 ± 0.2	1.89 ± 0.3	0.565
Bilateral ovarian cyst	2.14 ± 0.2	1.89 ± 0.3	0.565
Total (n = 35)	2.3 ± 1.8	1.68 ± 0.2	0.007*
Combined conservative and laparoscopy treatment			
Moderate and severe endometrioma laparoscopy surgery after 2 months treatment with dienogest from clinical and ultrasound diagnosis (n = 31)	3.11 ± 1.8	2.21 ± 0.2	0.005*
Unilateral ovarian cyst (n = 73)	3.13 ± 0.3	2.20 ± 0.2	0.352
Bilateral ovarian cyst (n = 56)	3.10 ± 0.5	2.22 ± 0.4	0.133

[a]using paired t-tests, *p < 0.05

Biomarker CA-125 changes

Table 5-8 shows the participants' CA-125 marker difference between before and after the treatments. The average level of CA-125 was 76.7 ± 1.33 IU/ml before the treatments and decreased to 28.9 ± 2.36 IU/ml after treatment (p = 0.689, n = 129). The average CA-125 level was 76.7 ± 1.33 IU/ml before drug treatments. However, CA-125 level seemed to drop more after treatment in Group II patients (34.8 ± 11.93 IU/ml, n = 42) than in Group I (17.3 ± 5.68 IU/ml, n = 21). In Group IV, average CA-125 marker was 96.6 ± 36.6 IU/ml and it decreased after surgery to 25.71 ± 2.96 IU/ml (p = 0.316). Additionally, CA-125 decreased in group III after surgery from 102 ± 29.1 IU/ml to 29.2 ± 4.15 IU/ml (p = 0.689) (Table 7).

Table 7. CA-125 marker difference before and after treatment (n = 129)

		Treatment Groups		
		Before (IU/ml)	After (IU/ml)	[a]p-value
Groups	Treatment methods	Mean ± SD	Mean ± SD	
Group I	Dienogest (n=42)	37.9 ± 5.25	20.6 ± 2.03	0.011*
Group II	Ibuprofen (n=21)	69.9 ± 9.79	35.1 ± 6.76	0.060
Group III	Dienogest for 3 months after surgery (n=35)	102 ± 29.1	29.2 ± 4.15	0.689
Group IV	Dienogest for 2 months before surgery (n=31)	96.6 ± 36.6	25.71 ± 2.96	0.316

[a]using paired t-tests, *p < 0.05

Table 8. Multiple Logistic Regression Analysis Model on factors associated with abnormal anti-müllerian hormone levels.

Variables	OR	95% CI	p-value
Age	1.04	0.92-1.02	0.188
Age by group			
20 - 24	1.00		
25 - 29	0.47	0.13 - 1.63	0.234
30 - 34	0.78	0.20-3.01	0.714
35-39	1.83	0.59-5.72	0.297
≥ 40	0.51	0.19 - 1.38	0.182
Ethnicity			
Khalkh	1.00		
Kazak	0.77	0.11 - 5.67	0.800
Other	2.00	0.24 - 11.1	0.395
Marital status			
Married	1.00		
Partner	0.54	0.13 - 2.21	0.390
Single	1.19	0.34 - 4.20	0.783
Duration of menstrual cycle	0.98	0.93 - 1.04	0.527
Menses duration	1.04	0.91 - 1.19	0.592
Average amount of blood	1.01	0.99 - 1.01	0.359
Age of first period	1.24	0.93 - 1.64	0.134
Menstrual cycle			
Regular	1.00		
Irregular	2.04	0.63 - 6.61	0.235
Number of live births			
None	1.00		
1 - 3	1.36	0.66 - 2.83	0.406
≥ 4	0.78	0.20 - 2.99	0.716
Sexually Transmitted Disease			
No	1.00		
Yes	1.04	0.79 - 3.30	0.325
Right follicle	0.99	0.98 - 1.01	0.136
Left follicle	1.01	0.99 - 1.02	0.531
Body Weight	1.02	0.98 - 1.05	0.499
Hormone Therapy			
No	1.00		
Yes	1.60	0.77 - 3.33	0.213

*$p < 0.05$

Discussion

In this study, we showed that three months of progestin treatment before surgery more effectively prevented endometriosis recurrence and maintain ovarian reserve than surgery without progestin treatment. Moreover, there were no statistical differences in ovarian reserve between those receiving progestin and NSAID. However, abdominal pain during menses and chronic pelvic pain were reduced in Group I patients who received synthetic progestin.

In clinical practice in Mongolia, the progestin treatment had a higher cost than surgery and NSAID treatment. However, receiving progestin before surgery decreased the hemorrhage during surgery, more effectively maintained the ovarian reserve and reduced the surgical duration. Several types of tests evaluate the ovarian reserve, including AMH level and the number of antral follicles. Raffi et al. have done meta-analysis to determine AMH effect on endometriosis surgical treatment. They reported the AMH level was significantly decreased after the surgery (weighted mean difference: 1.13; 95% CI: -0.36-1.88). Also, Urman et al. studied number of antral follicles and AMH levels before, immediately after surgery and 6 months after surgery.

AMH and antral follicle numbers were reduced by 24% and 11% immediately after the surgery. After 6 months, AMH and antral follicle numbers decreased by 24% and 15%. This reduction was not associated with the use of bipolar electrocoagulation [13, 40].

Furthermore, some studies reported AMH levels correlated with the endometrioma's characteristics. Wang et al. showed long term reduction of AMH levels in patients with large cysts in both ovaries and stage 4 endometriosis. Additionally, AMH levels decreased more with the use of electrocoagulation [36, 41]. Treatment before surgery is still debatable. Brown et al. have done a Cochrane review to investigate the efficacy of conservative treatment after surgery. They concluded there were no statistically significant results with conservative treatment and they couldn't identify any evidence that progestin treatment increases the possibility of becoming pregnant [42].

There are several limitations to this study. Our relatively small sample size and the absence of long-term term follow up were the main limitations. We did not evaluate the patients' satisfaction or long-term recurrence. Furthermore, we need to investigate endometrioma in infertility patients separately.

Conclusions

The reduction of AMH levels and the ovarian reserve was lower in groups treated by progestin and NSAID. The AMH level decreased more in the group treated by laparoscopic surgery without synthetic progestin treatment before surgery. The CA-125 marker decreased less in the group treated with NSAID than other groups of patients. The CA-125 marker was decreased similarly in the other 3 groups of patients.

Conflict of Interest

The authors state no conflict of interest.

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