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Comparison of suppressive hormonal therapy (low dose oral contraceptive) and aspiration in regression of ovarian endometrioma

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Background: **Endometriosis is a benign estrogen-dependent disease which is diagnosed through presence of endometrial tissue (secreting glands and stroma) outside the uterus. It affects nearly 5-10% of women of productive age in the US and with an increasing rate of incidence over the last years. There is disagreement over treatment of ovarian endometrioma and its dependent on various factors including pretreatment ovarian reserve, cystic location, patient's age and previous therapies. Since medical therapies such as oral contraceptives reduce the symptoms of ovarian endometria, different surgical therapies also have been proposed; however, as most of these methods end in lowered ovarian reserve, this study was conducted to investigate and compare the effects of LD contraceptive with aspiration in regression of ovarian endometria.** ***Methods and materials:*** **This clinical trial was conducted on 50 women aged 15-45 years who had referred to Al-Zahra Hospital with the ultrasound diagnosis of unilateral ovarian endometrioma≤6 cm and CA 125test <100 unites/ml. Written consent was obtained and the participants were randomly assigned to drug therapy and cyst aspiration groups. The former received one LD contraceptive tablet daily for 3 consecutive months and in the latter, ultrasound-guided cyst aspiration was conducted by an infertility subspecialist. All of the patients were followed up for 6 months in terms of clinical symptoms and cyst regression/recurrence. The data were analyzed in SPSS 25.** ***Results:*** **Findings showed that post-treatment clinical state of the patients (dyspareunia, dysmenorrhea and pelvic pain) was generally improved in both groups, but dysmenorrhea and pelvic pain decrease was significantly higher in those received LD contraceptive pills. The rate of cyst recurrence over 6 months was significantly higher in the aspiration group (0% in the drug therapy group vs 44% in the aspiration group, P-value< 0.001).** ***Conclusion:*** **The results showed that both treatment modalities were beneficial in short term improvement of clinical symptoms of endometriomas, while in long term hormone therapy had better outcome, it seems that the best therapeutic solution is to use mixed therapeutic methods. Nevertheless, further research is required on application of new drugs and mixed therapies.**

INTRODUCTION

Endometriosis is a benign estrogen-dependent disease which is diagnosed through presence of endometrial tissue (glands and stroma) outside the uterus (1, 2). It affects nearly 5-10% of women of productive age in the US (3, 4) and 10-15% in the word (9) and about 8-10% in Iran (10). Endometriosis may manifest as peritoneal implants, adhesions, deep infiltrative lesions, or ovarian endometrioma (5).It should be suspected in women with infertility, dysmenorrhea, dyspareunia, or pelvic pain. In mature women, occurrence of dysmenorrhea after years of pain-free menstruations is a special symptom of endometriosis (2).

The risk factors for endometriosis include short menstrual cycles, heavy menstrual bleeding, and prolonged bleeding (through backwards bleeding) (5). The gold standard test for diagnosis of ovarian endometrioma is laparoscopy (1). Therapies suggested for endometriosis include medical and surgical therapies (6). Oral contraceptives and progesterone's are considered first-line drug therapies (5).

The main goal of treating endometriosis is reducing the concurrent pain. This can be achieved through surgery or medical treatments while a combination of the two is needed for many patients (7). Currently, medical treatments rely on the fact that endometriosis is an estrogen-dependent disease and that there is a strong relationship between estrogen and the inflammatory environment associated with endometriosis (8). Medical therapies function as two mechanisms: anti-inflammatory and hormonal (7).

Nonsteroidal anti-inflammatory drugs are generally used for women with dysmenorrhea (11,12). Hormonal drugs used for endometriosis pain include hormonal contraceptives, progesterone and anti-progesterone, GnRH agonists, and aromatase inhibitors (7). Surgical therapies suggested for ovarian endometrioma include laparoscopic cystectomy, cyst aspiration, endometriosis laparoscopic ablation, and ablation-cystectomy combination (1,2). Aspiration is a noninvasive technique that uses transvaginal ultrasound for identifying the cystic location. The cystic fluid is aspirated with a syringe in this method. Three common side-effects are recurrence, infection and adhesion (1).

Although the standard treatment for endometrioma is surgery, it will reduce the ovarian reserve and because of the current interest in maintaining the ovarian reserve, the tendency is more toward

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conservative methods. Therefore, this clinical trial was conducted to compare a suppressive hormonal therapy with endometrial aspiration in the regression of cyst size and clinical symptoms of patients.

MATERIALS AND METHODS

This clinical trial is an interventional study that was conducted between 2016-18 in Tabriz's Al-Zahra Hospital, University dependent tertiary hospital.

Participant selection

This clinical trial was conducted on 15-45-year-old women who had referred to Al-Zahra Hospital with the ultrasound diagnosis of unilateral ovarian endometrioma≤6 cm and CA125 test <100 unites/ml. Written consent was obtained and the participants were randomly assigned to one of the following groups:

Group A) *suppressive hormonal therapy*: the patients received one LD contraceptive tablet (0.03mg ethinyl estradiol, 0.15mg levonorgestrel)* daily for 3 consecutive months and ultrasound scan was conducted at the end of this period for cyst regression. The patients were then followed up for 3 months in terms of cyst regression or occurrence. A questionnaire was administered to the patients at the beginning of the treatments and then 1, 3 and 6 months after the treatments. It measured the improvement of clinical symptoms (dysmenorrhea, dyspareunia, and pelvic pain) and regression or occurrence of the cyst.

Group B) *aspiration*: ultrasound-guided cyst aspiration was conducted by an infertility subspecialist and the ultrasound scan was performed again 3 and 6 months after the aspiration to examine possible cyst formation. A questionnaire was administered at the beginning of the study and 1, 3 and 6 months after the aspiration to measure the improvement of clinical symptoms, occurrence of the cyst or the need to repeat aspiration.

The patients were divided by means of block randomization using the specialized software. Researcher/patient blinding was not feasible in this study. Visual scale was used for assessing the clinical symptoms. The research proposal was approved in 2016/08/29 in the 213rdmeeting of the Ethics Committee (Ethical code IR.TBZMED.REC.1395.572, https://irct.ir/trial/5977).

Sample size was determined by means of the following formula:

$$n \geq \frac{2\sigma^{*2}\left(z_{\frac{\alpha}{2}} + z_{\beta}\right)^2}{\Delta^2}$$

Where σ^{*2} is the sum of variance components, Δ is diagnostic of clinically significant difference, α is level of significance, $1-\beta$ is test power.

Considering the previous studies and to increase the accuracy, the following values were applied:

$$\sigma^{*} = 2/4 \quad \Delta = 2/5 \quad \alpha = 0/05 \quad 1-\beta = 0/9$$

Therefore,

$$n \geq \frac{2 \times 2/4^2 (1/96 + 1/28)^2}{2/5^2} = 19/37$$

To be on the safe side, the sample size was set at 25 for each group. The primary outcomes in this study were regression of cyst size and improvement of clinical symptoms including dysmenorrhea, dyspareunia and pelvic pain.

Inclusion criteria were1) 15-45 years of age, 2) ultrasound diagnosis of unilateral ovarian endometrioma≤6 cm, 3) CA125 test <100 unites/ml. Exclusion criteria were: 1) possibility of malignancy, 2) endometriosis diagnosis in mother's ultrasound scan, 3) contraindications of taking LD tablet.

Statistical analysis of the findings

Kolmogorov-Smirnov test was used to assess the normality of data distribution. All of the normal quantitative data were reported as mean±SD and the abnormal ones were reported as median (25 percentiles, 75 percentile). Chi-square test was used to compare the qualitative variables and the results were reported as frequency (percent). For comparison of the abnormal quantitative variables between the two groups, nonparametric Mann-Whitney test was used. Nonparametric Friedman test was used for intragroup comparison of those variables. The normal quantitative variables were compared between the two groups using independent t-test and repeated measures ANOVA was used for intragroup comparison. The data were analyzed in SPSS 25.

RESULTS

The titles group A and group B are used to refer to suppressive hormonal therapy (LD tablet) group and aspiration therapy group respectively. Results of the independent t-test (table 1) showed no statistically significant difference between the two groups in terms of age (p=0.22), weight (p=0.73), height (p=0.64) and BMI (p=0.74). According to the Mann-Whitney test (table 2), there was no statistically significant difference in gravida (p=0.11) and abortion (p=0.80) between the two groups, but the difference was statistically signification parity (p=0.03) and number of live-born's (p=0.04).

Results of the chi-square test showed no statistically significant difference between the two groups prior to the beginning of the study in terms of menstrual state (p=0.76). Results of the chi-square test showed a significant improvement in menstrual state of the aspiration group and a significant occurrence of amenorrhea in the OCP group one month after the therapies (p<0.001). Results of the chi-square test three months after the therapies showed a significant difference in the menstrual state of the two groups (p<0.001). Compared to the first month, the aspiration group significantly developed menstrual disorders, mostly oligomenorrhea and metrorrhagia, at this stage. Results of the chi-square test six months after the therapies showed no significant difference between the two groups in terms of menstrual state (p=0.51). Nonparametric Mann-Whitney test was used for comparing the variables pelvic pain, dysmenorrhea and dyspareunia between the two groups and nonparametric Friedman test was used for intragroup comparison of these variables.

The Friedman test results revealed that both A and B therapies made statistically significant changes in pelvic pain, while the Mann-Whitney test had shown no significant difference in pelvic pain at the beginning of the study (p-values above 0.05). The Mann-Whitney test results showed that one month after the study, pelvic pain was significantly decreased in the aspiration group in comparison to the OCP group (p-values below 0.05). The results also showed that OCP and aspiration had the maximum effect after three months and one moth respectively.

According to the Mann-Whitney test, there was no statistically significant difference between the two groups in the severity of dysmenorrhea at the beginning of the study, while the difference became statistically significant one, three and six months after the therapies (p-values are below 0.05 for the three time periods). The Friedman test

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Table 1 Mean and frequency distribution of the demographic variables

P-value *	B (mean±SD)	A (mean±SD)	Variable
0.22	32.32 ± 4.64	34.04 ± 5.04	Age(year)
0.73	68.11 ± 7.54	68.95 ± 9.23	Weight(kg)
0.64	161.35 ± 3.03	160.85 ± 4.31	Height(cm)
0.74	26.18 ± 2.90	26.47 ± 3.18	BMI
Independent sample T-test			

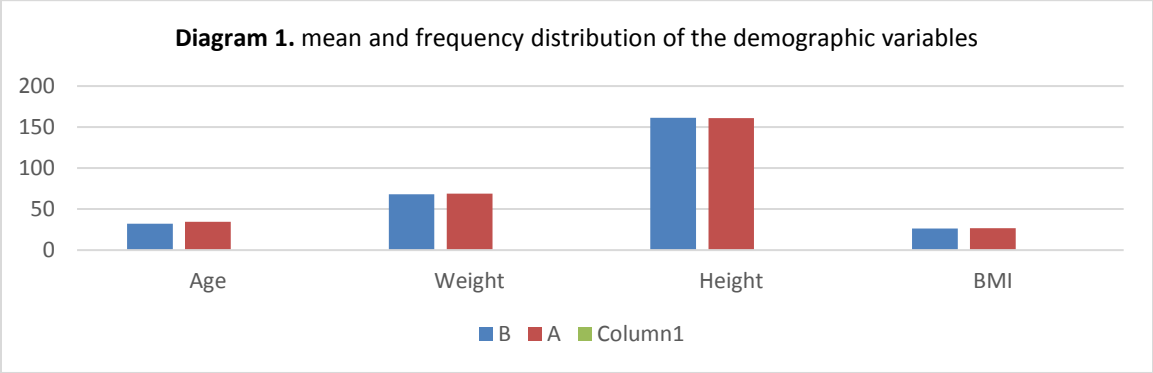
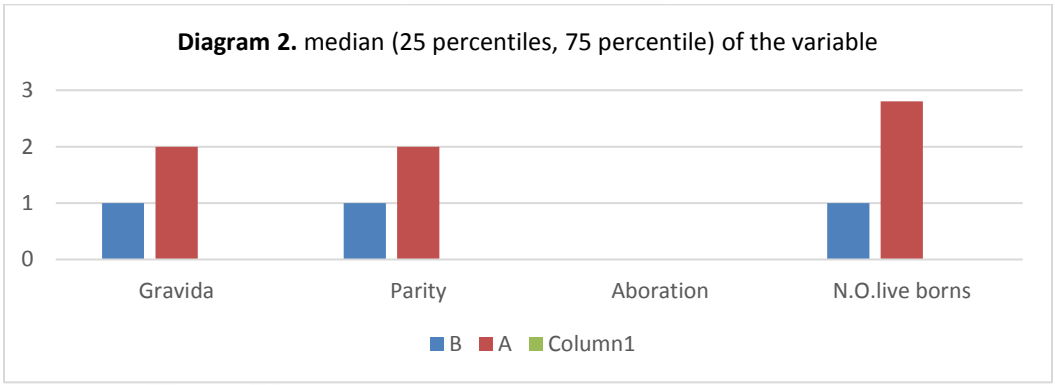


Table 2 Median (25 percentiles, 75 percentile) of the variables

P-value*	B	A	Variable
0.11	1.00 (0.00, 2.00)	2.00 (1.00, 3.00)	Gravida
0.03	1.00 (0.00, 1.00)	2.00 (1.00, 2.00)	Parity
0.80	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	Abortion
0.04	1.00 (0.00, 2.00)	2.00 (1.00, 2.00)	Number of live-born's
Mann-Whitney U Test			



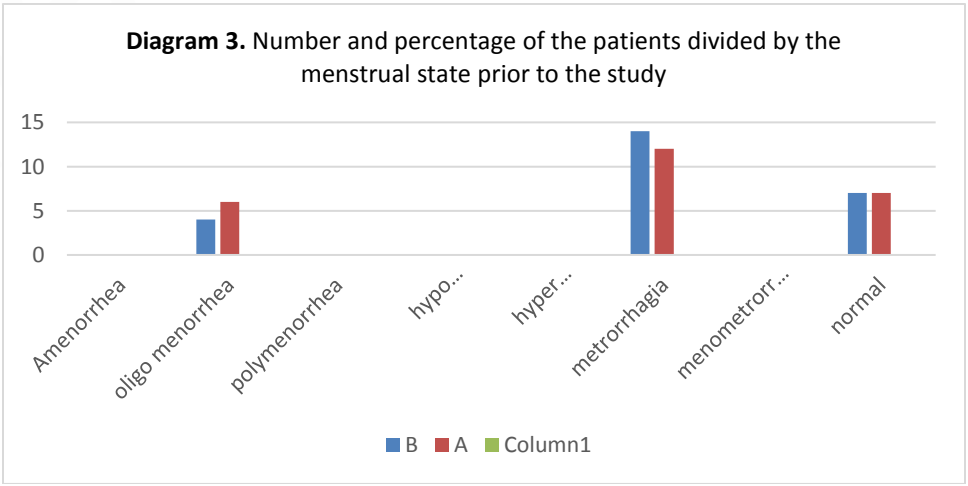


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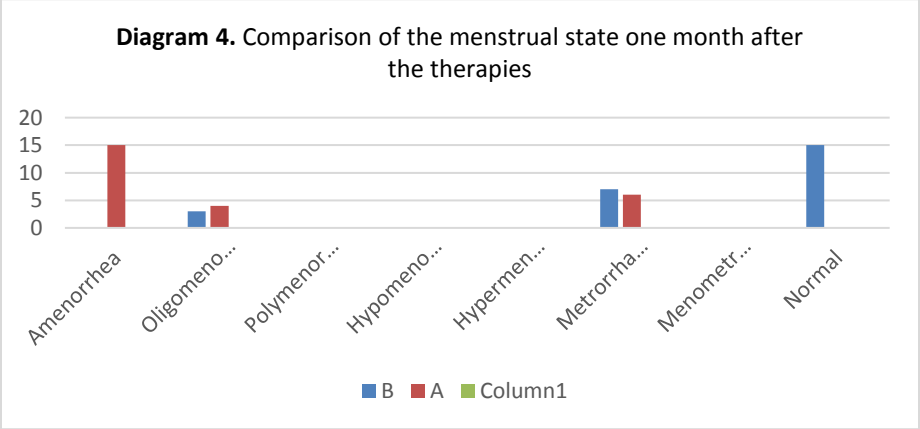
Table 3 Number and percentage of the patients divided by the menstrual state prior to the study

B	A	Menstrual state
0 (0.0%)	0 (0.0%)	Amenorrhea
4 (16.0%)	6 (24.0%)	Oligo menorrhea
0 (0.0%)	0 (0.0%)	Polymenorrhea
0 (0.0%)	0 (0.0%)	Hypo menorrhea
0 (0.0%)	0 (16.0%)	Hypermenorrhea
14 (56.0%)	12 (48.0%)	Metrorrhagia
0 (0.0%)	0 (0.0%)	Menometrorrhagia
7 (28.0%)	7 (28.0%)	Normal
χ^2 **test**		

Table 4 Comparison of the menstrual state one month after the therapies

B	A	Menstrual state
0 (0.0%)	15 (60.0%)	Amenorrhea
3 (12.0%)	4 (16.0%)	Oligomenorrhea
0 (0.0%)	0 (0.0%)	Polymenorrhea
0 (0.0%)	0 (0.0%)	Hypomenorrhea
0 (0.0%)	0 (0.0%)	Hypermenorrhea
7 (28.0%)	6 (24.0%)	Metrorrhagia
0 (0.0%)	0 (0.0%)	Menometrorrhagia
15 (60.0%)	0 (0.0%)	Normal
χ^2 **test**		



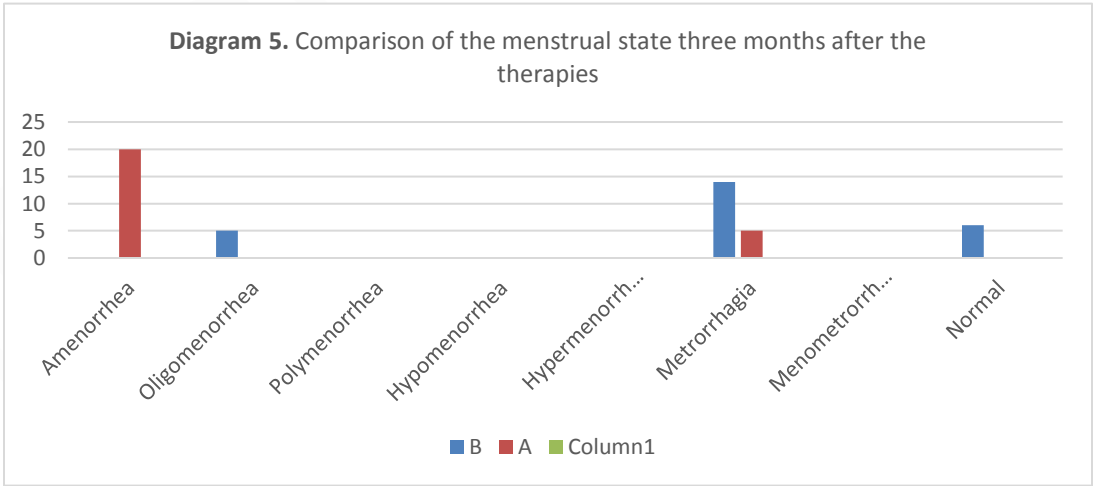


Table 5 Comparison of the menstrual state three months after the therapies

B	A	Menstrual state
0 (0.0%)	20 (80.0%)	Amenorrhea
5 (20.0%)	0 (0.0%)	Oligomenorrhea
0 (0.0%)	0 (0.0%)	Polymenorrhea

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0 (0.0%)	0 (0.0%)	Hypomenorrhea
0 (0.0%)	0 (0.0%)	Hypermenorrhea
14 (56.0%)	5 (20.0%)	Metrorrhagia
0 (0.0%)	0 (0.0%)	Menometrorrhagia
6 (24.0%)	0 (0.0%)	Normal
χ^2 **test**		

Table 6 Comparison of the menstrual state six months after the therapies

B	A	Menstrual state
0 (0.0%)	0 (0.0%)	Amenorrhea
6 (24.0%)	3 (12.0%)	Oligo menorrhea
0 (0.0%)	0 (0.0%)	Polymenorrhea
0 (0.0%)	0 (0.0%)	Hypomenorrhea
0 (0.0%)	0 (0.0%)	Hypermenorrhea
12 (48.0%)	15 (60.0%)	Metrorrhagia
0 (00%)	0 (0.0%)	Menometrorrhagia
7 (28.0%)	7 (280%)	Normal
χ^2 **test**		

Diagram 6. Comparison of the menstrual state six months after the therapies

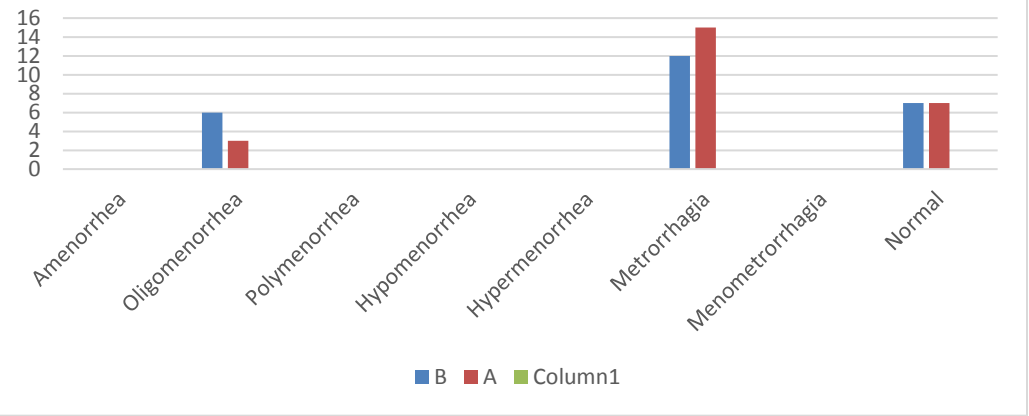

Table 7 Statistical analysis of the severity of pelvic pain at different periods

P-value *	B	A	Pelvic pain
0.052	5.00 (4.00-6.00)	6.00 (4.00-6.00)	Beginning of the study
<0.001	1.00(1.00-2.00)	4.00 (2.50-5.00)	One month
<0.001	3.00(2.00-3.50)	0.00 (0.00-2.00)	Three months
0.351	4.00(2.50-5.00)	3.00 (2.00-4.00)	Six months
	<0.001 **	<0.001**	
Mann-Whitney U Test; **Friedman test			

Table 8 Statistical analysis of the severity of dysmenorrhea at different periods

P-value*	B	A	Dysmenorrhea
0.35	4.00 (4.00- 6.00)	4.00 (2.00-5.00)	At the beginning of the study
0.03	2.00 (1.00-4.00)	2.00 (0.00-2.50)	One month
0.004	3.00 (1.00-4.00)	0.00 (0.00-2.00)	Three months
0.002	4.00 (1.00-4.00)	1.00 (0.00-2.00)	Six months
	<0.001**	<0.001**	
Mann-Whitney U Test; **Friedman test			

Table 9 Statistical analysis of the severity of dyspareunia at different periods

P-value *	B	A	Dyspareunia
0.069	4.00 (3.50-5.00)	3.00 (2.00-4.00)	At the beginning of the study
<0.001	0.00 (0.00-1.00)	3.00 (2.00-4.00)	One month
0.001	2.00 (1.00-3.00)	1.00 (0.00-2.00)	Three months
0.001	3.00 (2.00-4.00)	2.00 (2.00-2.50)	Six months
	<0.001**	<0.001**	
Mann-Whitney U Test; **Friedman test			

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Table 10 Cyst size at different periods

P-value *	B	A	Cyst size (mm)
0.20	48.63 ± 7.71	44.87 ± 12.06	At the beginning of the study
<0.001	10.83 ±14.48	35.51 ± 10.16	One month
0.02	17.27 ±13.92	26.23 ±14.49	Three months
0.85	28.27 ± 16.06	27.27 ±19.66	Six months
	<0.001**	<0.001 **	
** Repeated Measures ANOVA* Independent sample T-test			

indicated that both A and B therapies were able to significantly reduce the severity of dysmenorrhea with the decrease being significantly higher in the group who received drug therapy. The Mann-Whitney test results revealed that there was no statistically significant difference between the two groups in dyspareunia at the beginning of the study; however, the difference was statistically significant one, three and six months after the therapies (p-values are below 0.05 for the three time periods). The Friedman test showed that both A and B therapies were able to significantly reduce the severity of dyspareunia.

Results of the repeated measure ANOVA test showed that both A and B therapies were able to significantly reduce the cyst size. According to the independent t-test at the beginning of the study, there was no statistically significant difference in the cyst size between the two groups (p=0.20). The difference in the cyst size was statistically significant one and three months, but not six months after the therapies. Results of the chi-square test six months after the therapies showed a statistically significant difference in ultrasound outcomes between the two groups (p=0.006). The rate of recurrence was higher in the aspiration group. In relation to CA125, the mean scores of the two groups were in the normal range with no significant difference both at the beginning and at the end of the study.

DISCUSSION

The purpose of this clinical trial was to compare the effects of two conservative therapeutic methods on the improvement of clinical symptoms and regression of ovarian endometrioma in 50 patients. The results showed that both methods had a significant effecting improving the clinical symptoms including dysmenorrhea, dyspareunia, and pelvic pain. This was more noticeable at the end of the three-month course of treatment in the group who had received LD tablet. Cyst aspiration improved the clinical symptoms faster but the improvement was not persistent and recurrent endometrioma developed in 44% of the patients in six months. In a study by Muzii et al., (2012) titled "continuous versus cyclic oral contraceptives after laparoscopic excision of ovarian endometrioma's: a systematic review and meta-analysis", chronic pelvic pain and dyspareunia decreased in both the control and intervention groups, but there was no significant difference in the severity of pain between the two therapeutic methods. In their study on infertile women with ovarian endometrioma, Zhu et al., (2015) showed that cyst recurrence after the first aspiration of 91.5%, but only 5.4% of the patients developed recurrent cyst after repeated aspiration procedure (up to six stages).

Our results showed that the rate of endometrioma recurrence was lower in the drug-receiving group. In a study by Xiaoping Ke et al., (2015) titled "clinical analyses of endometriosis after conservative surgery", the recurrence rate was lower in the group who had received postoperative GnRH agonist treatment than two other groups who had received mifepristone or no postoperative treatment. Since in our study, cyst size reduction was much greater and faster in the aspiration group but recurrence was higher, it seems that combination of conservative surgery and suppressive hormonal therapy might be more effective.

A study by García-Tejedor et al., titled "ethanol sclera-therapy of ovarian endometrioma" showed that the recurrence rate was higher in the patients who had received sclera-therapy than the group who had received suppressive LD contraceptive tablet.

CONCLUSION

The main goals of different therapeutic solutions for endometrioma include reducing the possibility of endometriosis recurrence and side-effects, preserving the fertility, and increasing the quality of life and pain-relieving effects of the treatments. Although our results show that suppressive drug therapy is better than aspiration, but it could not meet our therapy goals; it seems that the best therapeutic solution is to use mixed therapeutic methods. However, further research and application of new drugs should be part of future treatment protocols. Since the aspiration group experienced much greater and faster reduction in cyst size, it is therefore recommended to be implemented in infertile women before ovulation induction.

Suggestions for future research

1. Similar studies with larger sample size for more robust results.
2. Comparison of hormonal and no hormonal medications.
3. Assessment of different surgical methods for endometriosis treatment.
4. Application of new antiangiogenic and anti-cell division drugs and even vitamins for endometriosis treatment.

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