

Comparison of the effectiveness of radical surgery with combination therapy (Sarem's Women Hospital protocol) in the management of severe endometriosis, a randomized controlled trial

ARTICLE INFO

Article Type

Clinical Trial

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Article History

Received: September 11, 2019

Accepted: November 05, 2019

e Published: December 17, 2020

ABSTRACT

Aim: This study was performed to compare the effectiveness of radical surgery and combination therapy (Sarem's Women Hospital protocol) and their costs in patients with grade IV (Severe) endometriosis.

Material and methods: In this randomized controlled trial, 44 patients with grade IV endometriosis were randomly divided into two groups. In the first group (n=19), all endometriosis lesions were completely removed by radical surgery. In the second group (n=25) no therapeutic surgery (except diagnosis) was performed and patients were included in the combination therapy treatment protocol. In this protocol (combination therapy), patients received 12 months of drug treatment with GnRH agonist (Decapeptyl 3.75 mg, IM Inj.) every 28 days. After the end of combination therapy, the early severe lesions of endometriosis (grade IV) degenerated very well and changed to grade one. By the second-look laparoscopy, fine adhesions or very poor remnants of endometriosis lesions removed easily. The severity of pelvic pain and dysmenorrhea was analyzed according to the VAS scale, one month and two years later, along with treatment costs in both groups.

Discussion and Conclusion: Combination treatment of endometriosis (Sarem's Women Hospital protocol) is more effective in reducing dysmenorrhea and pelvic pain one month and two years after treatment and with much fewer complications and is superior to radical surgery in terms of treatment costs.

Keywords: Endometriosis, Radical Surgery, Combination Therapy, Decapeptyl, Triptorelin, GnRH Agonist, Dysmenorrhea, Pelvic Pain, Recurrence, Cost, Randomized Controlled Trial (RCT)

Introduction

Endometriosis is a benign disease characterized by the presence of endometrial stroma outside the uterus (1, 2). It is a chronic disease of women that is difficult to diagnose based on clinical symptoms alone. The symptoms of endometriosis have a major overlap with other conditions such as irritable bowel syndrome and pelvic inflammatory disease, and its diagnosis as a definite result is often delayed, with a gap of several years between the onset of symptoms and definitive diagnosis (3). Endometriosis usually presents with symptoms such as dysmenorrhea, chronic pelvic pain, and infertility, and is one of the most common diseases of the female reproductive system that directly affects their physical, mental, and social life. About 10% of women of childbearing age have a mild to severe illness (4, 5). In fact, this disease is directly and strongly related to the rate of infertility and in general, its prevalence is much higher among infertile women than fertile women (6). Endometriosis is the third leading cause of hospitalization in women (7, 8) and one of the causes of hysterectomy surgery (9).

Endometriosis was first described by Rakitansky¹ in 1860, and since then various treatments such as analgesics, hormonal or surgical therapies, as well as combination hormonal therapy with surgery have been used, but so far no definitive cure has been found (10, 11). Studies show that the recurrence rate of the disease, after 5 years after surgical treatment, is about 20 to 50% (12, 13). Endometriosis can be managed with medication, surgery, or a combination of both. Past studies of all treatment strategies provide appropriate evidence, but their final effect and more appropriate treatment are still being studied, developed, and completed (14-16). To date, laparoscopy is considered an acceptable surgical method and the gold standard in the field of diagnosis, and one of the effective treatment methods for endometriosis (15, 17). On the other hand, the effect of drug therapies such as the use of GnRH agonist analogues in the treatment of endometriosis lesions has been reported (18-20). To date, there is no evidence that drug therapy is effective before endometrioma cysts are removed (21, 22). Since definitive treatment has not yet been approved, the need to develop and complete endometriosis treatment strategies is now well felt.

The aim of this study was to compare the effectiveness and cost of treatment between radical surgery and combination therapy (Sarem's Women Hospital protocol) in the treatment and management of endometriosis.

Material and Methods

In this randomized controlled trial study, 44 patients with severe endometriosis (grade IV) were enrolled according to the rASRM² guidelines, who had previously provided sufficient information about the study and their informed consent form had been approved and signed. These patients were randomly divided into two separate treatment groups using a random number table. (Figure 1)

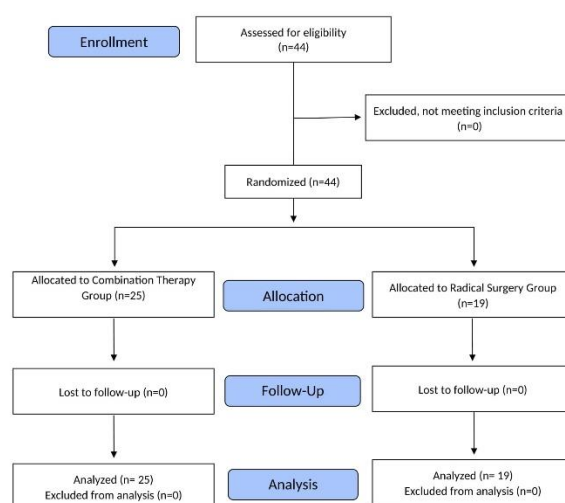


Figure 1. The CONSORT flow diagram of study³

¹ Karl Freiherr von Rokitansky

² The revised American Society for Reproductive Medicine

³ The CONSORT (CONSolidated Standards of Reporting Trials) 2010 guideline

In the radical surgery treatment group, 19 patients underwent extensive (radical) laparoscopic surgery and all superficial and deep lesions of endometriosis and lesions of the rectum, bladder or ureter were removed and necessary repairs were performed. In the combination therapy group (Sarem's Women Hospital protocol), for 25 patients, except primary laparoscopy for grading, no other surgical procedure was performed. They then received drug treatment with an intramuscular injection of Decapeptyl⁴ 3.75 mg (a long-acting GnRH agonist) every 28 days for 12 months. After the end of combination therapy, the early severe lesions of endometriosis (grade IV) degenerated very well and changed to grade one. By the second-look laparoscopy, fine adhesions or very poor remnants of endometriosis lesions removed easily. To reduce the side effects of medical treatment, add-back therapy and hormone replacement therapy were performed from the sixth month onwards.

At the beginning of the study and before the interventions, all patients were evaluated for pelvic pain and dysmenorrhea with visual analogue scale (VAS) measurement. This evaluation was performed on patients one month after the end of treatment and two years later to evaluate and compare the two groups in terms of the improvement of symptoms as well as recurrence of pelvic pain and dysmenorrhea.

Data collection and analysis were performed by a statistical consultant who did not know the type of division of individuals into two groups (study blinding). Data were analyzed by IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA). Frequency distribution tables were used to present the results of descriptive data and independent student's t-test, chi-square test and Fisher's exact test were used to analyze the analytical data and the significance level was considered 0.05.

Results

In this study, 19 female patients with severe endometriosis (grade IV) with a mean age of 35.84 years underwent radical surgery and another 25 patients (with grade IV of endometriosis) with a mean age of 35.64 years underwent combination therapy (Sarem's Women Hospital protocol). Statistically, there was no significant difference between age, height, weight, and body mass index (BMI) of the two groups ($P > 0.05$). (Table 1)

Table 1. Comparison of age, height, weight and body mass index			
Parameter	Combination Therapy Group (n=25)	Radical Surgery Group (n=19)	Mean Difference
	Mean (SD)	Mean (SD)	
Age (yr.) *	35.64 (5.02)	35.84 (3.80)	0.20
Height (cm) *	162.16 (5.79)	161.58 (5.52)	0.58
Weight (kg) *	63.68 (11.70)	65.74 (11.14)	2.06
Body Mass Index (kg/m ²) *	24.20 (4.06)	25.14 (4.84)	0.94

* There was no statistically significant difference between groups (Student's T-test, $P > 0.05$).

8.0% of women in combination group therapy were single and 92.0% of them were married. While in the radical surgery treatment group, these values were 26.3% and 73.7%, respectively. Also in Table 2, the percentage of pregnancy, live birth and abortion in both groups are presented. In none of the above cases was there a statistically significant difference between the two groups ($P > 0.05$).

⁴ Triptorelin (Generic Name)

Table 2. Comparison of marital status, pregnancy, live birth and abortion

Parameter	Combination Therapy Group (n=25) Number (Percent)	Radical Surgery Group (n=19) Number (Percent)
Marital Status *		
Single	2 (8.0%)	5 (26.3%)
Married	23 (92.0%)	14 (73.7%)
Gravidity *		
G0	14 (56.0%)	11 (57.9%)
G1	10 (40.0%)	7 (36.8%)
G2	1 (4.0%)	1 (5.3%)
Parity *		
P0	22 (88.0%)	13 (68.4%)
P1	3 (12.0%)	5 (26.3%)
P2	0 (0.0%)	1 (5.3%)
Abortion *		
A0	20 (80.0%)	16 (84.2%)
A1	5 (20.0%)	3 (15.8%)

* There was no statistically significant difference between two groups (chi-square test, $P > 0.05$).

According to the data obtained from the VAS scale (in the range of 0 to 10), the mean pelvic pain and dysmenorrhea in patients in both groups at the beginning of the study were not statistically significant different ($P > 0.05$). (Table 3)

Table 3. Comparison of pelvic pain and dysmenorrhea, at the beginning of the study (VAS Score)

Parameter	Combination Therapy Group (n=25) Mean (SD)	Radical Surgery Group (n=19) Mean (SD)	Mean Difference
Pelvic Pain *	8.30 (0.43)	8.50 (0.45)	0.20
Dysmenorrhea *	8.76 (0.35)	8.63 (0.36)	0.13

* There was no statistically significant difference between two groups (Student's T-test, $P > 0.05$).

The average pelvic pain one month after the end of treatment in the radical surgery group was 7.11, while in the combination therapy group (Sarem's Women Hospital protocol), it was equal to 1.96. There was a statistically significant difference between the two groups ($P < 0.05$), so that in the combination therapy group, pelvic pain was clearly reduced (Figure 2).

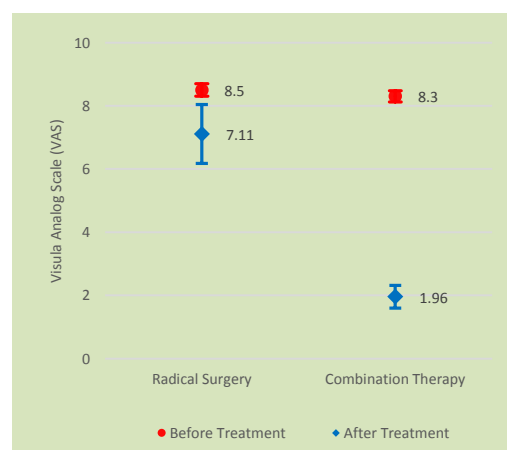


Figure 2. Comparison of pelvic pain, one month after treatment completion (Mean \pm SEM, $P < 0.05$)

Also, according to the same scale (VAS), the severity of dysmenorrhea one month after the end of treatment in the radical surgery group was 8.26, while the scale of dysmenorrhea in the combination therapy group (Sarem's Women Hospital protocol) was equal to 2.88, which was a significant statistical difference between the two groups ($P<0.05$), and dysmenorrhea was lower in the combination treatment group. (Table 4 and Figure 3)

Table 4. Comparison of pelvic pain and dysmenorrhea, one month after treatment completion (VAS Score)			
Parameter	Combination Therapy Group (n=25)	Radical Surgery Group (n=19)	Mean Difference
	Mean (SD)	Mean (SD)	
Pelvic Pain ¹	1.96 (1.81)	7.11 (4.09)	5.15
Dysmenorrhea ¹	2.88 (2.72)	8.06 (3.07)	5.18

¹ There was statistically significant difference between two groups (Student's T-test, $P<0.05$).

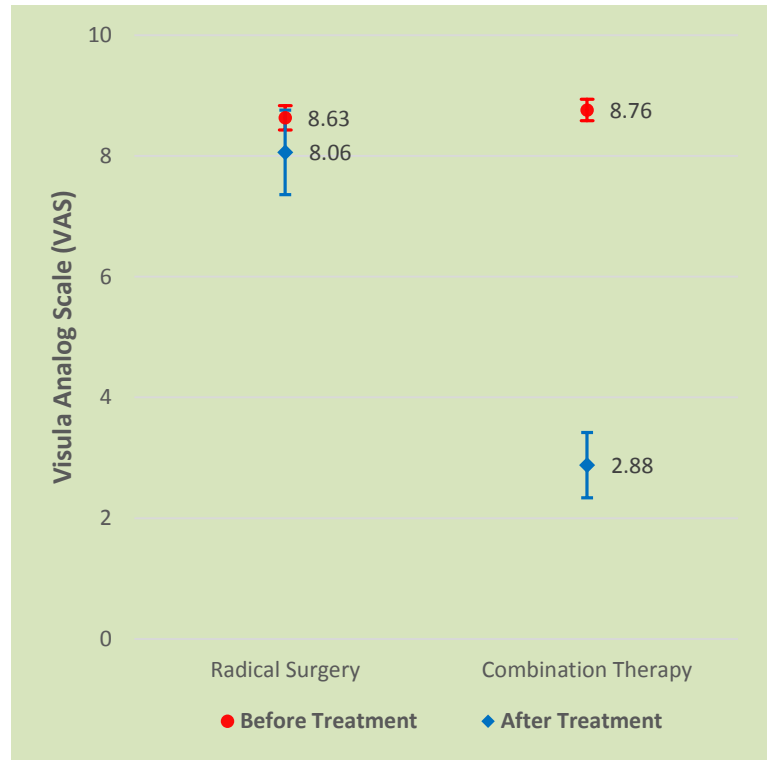


Figure 3. Comparison of dysmenorrhea, one month after treatment completion (Mean ± SEM, $P<0.05$)

To evaluate the severity recurrence of endometriosis symptoms and compare it between the two treatment groups, two years after treatment, the severity of pelvic pain and dysmenorrhea in both groups was measured and compared. According to the VAS scale, the pelvic pain score in the radical surgery group was 3.42, while in the combination therapy group (Sarem's Women Hospital protocol), it was equal to 1.12, which showed a statistically significant difference between the two groups ($P<0.05$), so that the severity recurrence of pelvic pain in the combination therapy group was clearly lower (Figure 4). Also, according to the same scale, the severity of recurrence of dysmenorrhea, two years after treatment in the radical surgery group was 4.58, while the scale of dysmenorrhea in the combination therapy group was 1.64, which was statistically significant between the two groups ($P<0.05$), and severity recurrence of dysmenorrhea was lower in the combination treatment group (Table 5 and Figure 5).

Table 5. Comparison of pelvic pain and dysmenorrhea, two years after treatment completion (VAS Score)			
Parameter	Combination Therapy Group (n=25)	Radical Surgery Group (n=19)	Mean Difference
	Mean (SD)	Mean (SD)	
Pelvic Pain ¹	1.12 (2.55)	3.42 (4.14)	2.30
Dysmenorrhea ¹	1.64 (2.52)	4.58 (3.91)	2.94

¹ There was statistically significant difference between two groups (Student's T-test, $P < 0.05$).

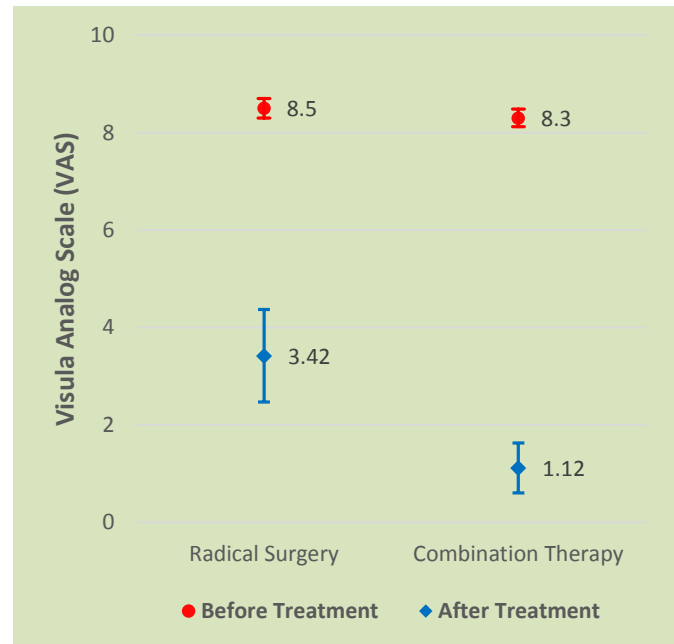


Figure 4. Comparison of pelvic pain, two years after treatment completion (Mean \pm SEM, $P < 0.05$)

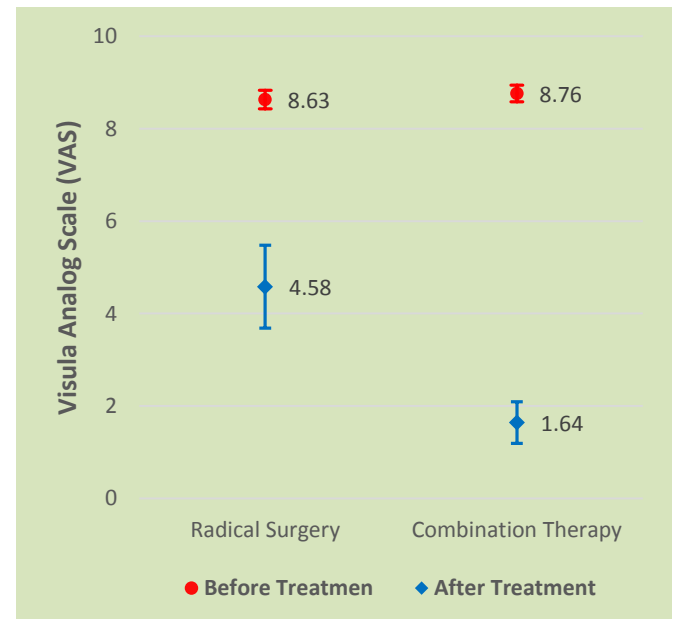


Figure 5. Comparison of dysmenorrhea, two years after treatment completion (Mean \pm SEM, $P < 0.05$)

In the combination therapy group (Sarem's Women Hospital protocol), no cases of post-treatment complications were seen, while 21.1% of people undergoing radical surgery had some type of post-treatment complications, which had a statistically significant difference between the two groups ($P < 0.05$). (Table 6) These complications included ureteral injury (one case), dyspareunia, endometrioma and severe abdominal pain (one case), colostomy and pelvic infection (one case), and vaginal fistula with urinary incontinence (one case).

Table 6. Comparison of post-treatment complications		
Parameter	Combination Therapy Group (n=25) Number (Percent)	Radical Surgery Group (n=19) Number (Percent)
Post-Treatment Complications ¹		
Yes	0 (0.0%)	4 (21.1%)
No	25 (100.0%)	15 (78.9%)

¹ There was statistically significant difference between two groups (Fisher's exact test, $P < 0.05$).

Finally, in terms of treatment costs, the combination therapy group (Sarem's women Hospital Protocol) incurred lower costs than the radical surgery group, 153.73 million rials (IRR) versus 236.72 million rials (IRR), which was also a statistically significant difference ($P < 0.05$). (Table 7)

Table 7. Comparison of treatment cost			
Parameter	Combination Therapy Group (n=25) Mean (SD)	Radical Surgery Group (n=19) Mean (SD)	Mean Difference
Treatment Cost ¹ (million rials, IRR)	153.73 (74.72)	236.72 (145.42)	82.99

¹ There was statistically significant difference between two groups (Student's T-test, $P < 0.05$).

Discussion

The results of this randomized clinical trial showed that combination therapy had better results than radical surgery in treating and reducing pelvic pain and dysmenorrhea in severe (grade IV) endometriosis. According to *Vercellini et al.* (23), surgery is still the best treatment for endometriosis with the least chance of recurrence, but on the other hand, it has been seen that repeated endometriosis surgery eventually leads to hysterectomy and more complications (24). Drug intervention along with surgery can be used as a treatment supplement to help reduce recurrence and reduce complications. However, many side effects of these drugs have been proven today, for example, high risk of mucosal damage, impact on the menstrual cycle and disruption of menstrual cycle, implantation interference, abnormal immune response, inflammation, increased apoptotic activity, and impact on future fertility, all of which lead to research into the availability of drug compounds with specific effects on abnormal endometrial cell synthesis and to destroy them. So far, many hormonal compounds have been introduced that can be used as adjunctive therapy in addition to surgery. For example, progesterone is one of the compounds prescribed as a drug treatment for endometriosis, but according to studies, about 9% of patients do not respond to this treatment, and no exact reason has been found yet. The new generation of drugs is aromatase inhibitors (AIs). The aromatase enzyme expressed in several tissues (breast, ovary, endometrium, placenta, testes, skin, bone, fat, and brain) that mediates the conversion of androstenedione to estrone and testosterone to estradiol. Because endometriosis is an estrogen-dependent disease and with high estrogen levels, the rate of proliferation and production of abnormal mucus increases, these drugs can be effective in controlling the progression of this disease. One of its side effects is local inflammation, because increased production of prostaglandins is a strong inducer of aromatase activity. The latest generation of drugs are GnRH agonists, which are very similar to endogenous GnRH (differing in only one or more amino acid lateral substitutions) that reduce the secretion of FSH and LH from the pituitary gland by reducing the activity of the hypothalamic-pituitary axis. Lack of secretion of these two hormones inhibits the secretion of sex hormones such as testosterone and estrogen from the gonads and plays an effective role in reducing the progression of endometriosis. Important side effects of this group

of drugs such as decreased bone density, decreased libido and hot flashes can be significantly controlled with the help of add-back therapy and hormone replacement therapy (HRT). The protective effect of add-back therapy is especially important in maintaining bone density. Today, many protocols are used in conjunction with the treatment of these drugs in addition to surgery (20,23,24). In our previous descriptive study, the therapeutic effects of using a GnRH agonist in the management of various degrees of endometriosis have been reported (16).

Schenken et al. (25) reported in 1982 that 90% of patients with mild endometriosis who had improved with surgery and whose ovulation problem had resolved with Clomifene Citrate, one year after treatment, became pregnant, so it seems that the combined use of conservative surgical methods and the use of drugs together can have effective results in controlling and improving the symptoms of endometriosis and also maintain fertility.

Because endometriosis is an estrogen-dependent disease that confirms the rarity of endometriosis before puberty or after menopause, and precise immunohistochemically studies have shown that almost all endometriosis lesions contain estrogen receptors, hormonal drugs such as GnRH agonists such as Nafarelin⁵ or Leuprolide⁶ can be effective in controlling the symptoms of endometriosis by inhibiting the production of gonadotropins (26). Studies have shown that treatment with GnRH agonists can reduce endometrioma rates by up to 51%. The dose of this drug is also very important, but in any case, the most effective treatment for severe cases is surgery and removal of endometrial lesions (27).

In another study conducted in 1992, between 1980 and 1990, the 579 women with endometriosis divided into four treatment groups (no treatment, drug therapy, laparoscopic surgery, and laparotomy), and the severity of the disease and its progression were examined. The results showed that in women with mild endometriosis, they responded to drug and laparoscopic treatments, but in severe degrees of endometriosis, laparoscopy had more positive results than any other group and the weakest results were related to the drug treatment group alone. In this study, the life table and fertility of the people were followed up to three years after treatment, that the best results were related to the laparoscopic group, which had the lowest amount of tubal adhesions. Therefore, laparoscopic treatment was suggested as a minimally invasive treatment with a shorter hospital stay, lower hospitalization costs, less stress in terms of a psychological condition, and shorter recovery time than other methods (28).

In the study conducted in 2013 by *Zhong et al.* (29), the efficacy and safety of GnRH agonists in combination with laparoscopic surgery in the treatment of moderate to severe endometriosis were compared. A number of patients underwent hormone therapy, surgery, or combination therapy (hormonal surgery). The results showed that the recurrence of patients' symptoms (including dysmenorrhea and dyspareunia) was lower in the combination therapy group and also the highest rate of disease regression was seen in the combination therapy group.

Another study by *Koga et al.* (30) in 2013 showed that in the treatment of endometrioma, patients were more likely to have a recurrence if they had received medication before surgery. However, treatment with a combination of GnRH agonists and oral contraceptive pill (OCP) after endometrioma surgery can have good therapeutic effects.

Overall, it seems that despite the many studies that have been done in this field, a single, generalizable protocol has not yet been introduced.

Conclusion

In the present study, the efficacy, complications and cost of two different treatment methods in severe endometriosis (grade IV), including radical surgery and combination therapy (Sarem's Women Hospital protocol) were evaluated and compared. The results showed that combination therapy has better successful results than radical surgery in improving the symptoms and reducing recurrence of severe endometriosis. Also, combination therapy has few side effects and on the other hand, its costs are much lower than radical surgery. Therefore, it can be considered as a practical treatment protocol in the management and treatment of severe endometriosis.

Conflict of interest

There was no conflict of interest in this study.

Acknowledgments

The authors appreciate the staff of Sarem's Women Hospital and Sarem's Fertility and Infertility Research Center (SAFIR), especially Dr. Maryam Mahmoudinia and Mrs. Maryam Naderi, as well as the participants.

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⁵ Synarel

⁶ Leuporelin, Lupron

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