DOI: https://doi.org/10.53350/pjmhs221611020

ORIGINAL ARTICLE

A Randomized Control Trial of Combined Surgical and Hormonal Therapy of Endometriosis

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ABSTRACT

Aim: To evaluate the three therapy strategies including surgical therapy, hormonal therapy, and combined treatment for the management of endometriosis

Study design: A multicentric randomized control trial

Place and Duration: This study was conducted in 6 different hospitals of Pakistan, Muhammad Medical and Dental College Ratanabad Mirpurkhas, Social Security Landhi Hospital Karachi, Sindh Government CDF Hospital , Bilawal Medical College for Boys Jamshoro, Ghulam Muhammad Mahar Medical College Sukkur, Bahria International Hospital Karachi, Sandeman Provincial Hospital Quetta Pakistan Pakistan from June 2020 to June 2021.

Methodology: The study included 360 participants with genital endometriosis. The age of the patients ranged from 18 years to 45 years. All the patients did not have any previous surgical intervention. The patients were randomly treated with one of the three treatments. A laparoscopic evaluation was done after three months of hormonal and combined therapy. Re-evaluation of surgically treated patients was done after 5 to 6 months. Stage of endometriosis, recurrence of symptoms, and the rate of pregnancy were noted in the re-evaluation phase of the study.

Results: The overall cure rate of all types of endometriosis was 56.11% after every regimen of treatment. The cure rate after treatment from combined therapy was 60%. Those treated exclusively by hormone therapy showed a cure rate of 54.17%. A total of 54.17% of patients were cured exclusively by surgical treatment. The rate of recurrence was lowest in the patients given combined therapy. Dyspareunia and dysmenorrhea were significantly reduced. The overall rate of pregnancy was 53% to 64%. The rate of pregnancy was not different among all the groups.

Conclusion: After giving hormonal therapy, surgical treatment, and combined treatment, it has been noticed that recurrence was lowest in the combined medical and surgical treatment group. The rate of pregnancy had also got better after all the means of treatment. The highest rate of cure was achieved by combined therapy.

Keywords: Endometriosis, laparoscopy, hormone therapy, combined treatment, infertility, recurrence

INTRODUCTION

Endometriosis is thought to be the second most intricate benign genital disease found in women followed by uterine myoma. It can be described as the presence of endometrial glands and endometrial stroma at an ectopic location, outside the epithelial lining of the cavum uteri. Common symptoms of endometriosis experienced by females suffering from endometriosis are dysmenorrhea, chronic pelvic pain, deep dyspareunia, subfertility, chronic fatigue, lower back pain, and dysfunctional uterine bleeding. The patient can also experience other symptoms such as bloating, rectal bleeding, constipation, dyschezia, hematuria, and diarrhea [1].

About 50% of teenagers and overall 32% of women of reproductive age that undergo operative intervention due or dysmenorrhea and chronic pelvic pain are diagnosed with endometriosis. A total of 9% to 50% of women who are operated for endometriosis had presented with infertility. However, the overall prevalence of endometriosis is indefinite due to diversity and non-specificity in its signs and symptoms [2]. An average time interval that has been noticed between the onset of symptoms and diagnosis in case of endometriosis is almost seven years. The average age at which this condition is diagnosed is between 20 to 40 years. In the case of secondary infertility, the frequency increases as the time since the last delivery increases [3]. Causal treatment for endometriosis is not available due to a lack of data on the pathogenesis of the disease. However, the options which can be used for the treatment of endometriosis are analgesia, expectant management, surgical intervention, hormonal therapy, and combined therapy. The growth of endometriosis is triggered by estrogen, hence, several medical therapies can be given [4].

The primary strategies of the treatment of endometriosis that have been administered were gestagens and then danazol was used later along with an analog of gonadotropin-releasing hormone (GnRH). Now, this therapy has been upgraded by the addition of progesterone. GnRH has several adverse effects such as vasomotor symptoms, mood swings, and bone demineralization. They are prevented by estradiol [5]. Further research on the inhibition of the interaction of mediators that are involved in the maintenance of vascularization, cell proliferation, and inflammatory

processes, is under focus. The mediators which are of great interest in this regard are selective cyclooxygenase-2 inhibitors (e.g., rofecoxib and celecoxib) and aromatase inhibitors (e.g., exemestan, anastrozole, and letrozole) [6].

Endometriosis is capable of disrupting the anatomy of the reproductive organs of a female. Hence, surgical treatment has great significance. In the advanced stages of the disease, organ damage can lead to subfertility, fibrosis, adhesions, and extreme pain. These consequences demand surgical intervention. Laparoscopic intervention can prevent an early diagnosis and delay the progression of the symptoms. Disadvantages and risk factors of laparoscopic intervention are organ damage, post-operative complications, and the formation of adhesions [7]. The recurrence rate of endometriosis is 20 to 40% after 5 years of treatment. Oral contraceptive pills, progesterone intrauterine device (IUD), or any other suppressive hormonal therapy has shown a reduction in the rate of recurrence and suppression of the pain associated with endometriosis [8].

The combined surgical and hormonal therapy involves diagnostic laparoscopy that includes removal of endometrial foci and a six months endocrine hormonal therapy. The surgery also comprises residue foci, organ reconstruction, and adhesiolysis [9]. The objective of the present study was the determination of the most effective type of endometriosis therapy.

METHODOLOGY

This was a multicentric randomized controlled trial included a total of 360 participants who had been diagnosed with endometriosis. Permission was taken from the ethical review committee of the institute. The range of age of the patients was from 18 years to 45 years. The patients were randomly allocated into three groups of treatment. The present study included medical therapy, surgical therapy, combined therapy, and a second-look operation. Written informed consent was taken from all the patients after a description of the mode of treatment.

The groups were allocated with 120 patients in each group. First of all, the symptoms of the patients were analyzed. The patients were examined through a pelviscopy. A total of 330 out of 360 patients had come back for a second-look laparoscopy. The remaining 30 patients did not return for the laparoscopy. Those patients who had undergone surgery for endometriosis and had been treated for the disease previously by hormonal therapy were not included in the study. The diagnosis of endometriosis was made based on laparoscopy and the rating was done according to the Endoscopic Endometriosis Classification (EEC). This system has been introduced by Liselotte Mettler and Kurt Semm [10].

A tissue sample from the ectopic endometrium was obtained from the patients who had a diagnostic hysteroscopy. The samples were also taken during the laparoscopic treatment given for endometriomas. Cryostat sections were prepared and hematoxylin-eosin stains were given. The histopathological evaluation confirmed the origin, proliferation, and cyst wall of endometriosis.

The Group 1 (n=120) patients underwent laparoscopy for the diagnosis and hormonal therapy was given with 3.75mg leuprorelin acetate. The hormone was injected subcutaneously every month for three consecutive months. The drug is a GnRH agonist. Group 2 (n=120) underwent laparoscopy for the treatment of endometriosis. No hormonal therapy or any medical therapy was provided to these patients. The surgery comprised of removal of adhesions, excision of the endometriosis foci, and correction of the normal anatomy of the reproductive organs. Those patients who had complained of infertility were checked for tubal patency and they were also given chromopertubation on the second-look laparoscopy. The Group 3 (n=120) patients underwent surgical laparoscopy and they were given hormonal therapy after the surgery. The hormonal therapy was the same that was given to the participants of Group 1 and for the same period of time.

The second-look laparoscopy was done in Group 1 and Group 3 after 1 to 2 months of the treatment. In Group 2, the follow-up laparoscopy was performed 5 to 6 months followed by the surgical treatment. The patients were called for regular follow-up visits for 1 year to regularly monitor them for the recurrence of the symptoms and disease. Those patients that were trying to conceive, were called for a follow-up visit for two years. The data were analyzed using IBM SPSS version 26.

RESULT

The treatment had improved the EEC stage of all three groups. The rate of cure was higher in Group 3 as compared to Group 1 and Group 2. Table 1 shows the improvement in the stage in all three groups. The down-staging of the endometriosis was confirmed through laparoscopy on the follow-up visit. To evaluate the rate of recurrence, the patients were monitored through regular follow-up visits. Their symptoms were recorded and analyzed for one year. This was done to analyze the effect of all three treatments on the rate of recurrence. The data for all the groups was not significantly different. The results are given in Table 2

Table 1: Improvement of the stage of endometriosis

Variable		EEC Stage Number (Percentage)			
		0	1	2	3
Group 1 (Hormone therapy) N=120	Before therapy	0	48 (40)	46 (38.33)	26 (21.67)
	After therapy	65 (54. 17)	38 (31.67)	11 (9.17)	6 (5)
Group 2 (Surgery) N=120	Before therapy	0	60 (50)	38 (31.67)	22 (18.33)
	After therapy	65 (54. 17)	16 (13.33)	28 (23.33)	11 (91.7)
Group 3 (combined therapy) N=120	Before therapy	0	63 (52.5)	29 (24.17)	28 (23.33)
	After therapy	72 (60)	22 (18.33)	20 (16.67)	6 (5)

Though recurrence of symptoms was seen in all the groups, it can still be seen that the symptoms had improved significantly. The greatest efficacy was seen in the combined treatment group. The overall recurrence rate was also lesser in the combined treatment group. The third measure was the rate of pregnancy. The patients that were

interested in conceiving were monitored for 2 years. The pregnancy rate was 53% to 64% in all the treatment groups. A comparison of the rate of pregnancy is given in table 3. The rate of pregnancy after an exclusive treatment with surgery was 53% and it is comparatively less than Group 1 and Group 3. In the framework of the present study, it has been observed that the most successful regimen of treatment is hormonal therapy combined with surgical treatment. The combined treatment tended to have an increased cure rate, decreased recurrence of the symptoms, and improved pregnancy rate.

Table 2: Recurrence of symptoms within one year of the treatment

Variable		Recurrence symptoms n (%)		
		Dysmenorrhea	Dyspareunia	Abdominal pain
p-value before symptoms		0.600	0.060	0.050
p-value after symptoms		0.050	0.007	0.280
Group 1 (Hormone therapy) N=120	Before therapy	72 (60)	67 (55.83)	58 (48.33)
	After therapy	34 (28.33)	26 (21.67)	31 (25.83)
Group 2 (Surgery) N=120	Before therapy	68 (56.67)	60 (50)	50 (41.67)
	After therapy	24 (20)	18 (15)	29 (24.17)
Group 3 (combined therapy) N=120	Before therapy	65 (54.17)	61 (50.83)	50 (41.67)
	After therapy	19 (15.83)	10 (8.33)	20 (16.67)

Table 3: A comparison of the rate of pregnancy in all the treatment groups

Variables	Pregnancies	Live Births	Extra-uterine pregnancies	Abortions
P-value	0.250	0.284	0.654	0.954
Group 1 (Hormone therapy) N=120	77 (64%)	66 (55%)	3 (2.5%)	10 (8.33%)
Group 2 (Surgery) N=120	64 (53%)	54 (45%)	1 (8.33)	11 (9.17%)
Group 3 (combined therapy) N=120	70 (58.5%)	60 (50%)	2 (1.67%)	11 (9.17%)

DISCUSSION

In the present study, there were 360 patients with endometriosis. The ages of the patients ranged from 18 years to 45 years. They were randomly allocated into three groups according to the mode of the treatment given to them (hormonal, surgical, and combined). The success rate of all the groups was evaluated. All three regimens of treatment reached an overall cure rate of 56.11%. However, the rate of recurrence was lowest in the combined treatment group. This group had an overall high efficacy in the treatment of endometriosis [10].

The hormonal therapy can be given before surgical intervention to decrease the stage and size of the endometriosis. This strategy also makes the surgery easier. Nonetheless, there is no research evidence regarding the preoperative administration of hormonal therapy and its beneficial effects in terms of ease in the surgery. Some trials have reported a longer pain relief period and lesser recurrence of the symptoms using hormonal therapy after the surgery [11]. According to the study of Schweppe et al, pelviscopic treatment does not treat the active cases of endometriosis alone. Some combined treatment is necessary for the active disease [12].

A high statistical difference could be seen between the combined treatment group and the exclusive surgical treatment group. According to the study of Regidor et al, a significant improvement was observed after administration of triptorelin, a GnRH analog. Their study showed that 63% of patients had no endometriosis after the treatment. 30% of them had stage 1 and only 7% were left with stage 2 of the disease. No Patient was left with stage 3. They had used the ASF classification of endometriosis. Buserelin, another GnRH analog, decreased the ASF score from 17.4 to 7.2 when the treatment was combined with the surgical intervention [13]. These findings were consistent with the findings of the present study. Although many patients had reported relief of symptoms by hormonal therapy, hormonal therapy alone is not sufficient for enhancing fertility, removal of adhesions, and diminishing pelvic masses. However, the results of the present study show lesser recurrence in the combined therapy group compared to the study of Regidor. The pregnancy rate of the present study was also comparable to their study. As the study of Schweppe et al, the present study also shows a lower rate of recurrence after administration of combined therapy [12]. According to the study of Zupi et al, the patients treated with GnRH antagonists showed a significant reduction in symptoms such as dysmenorrhea, dyspareunia, and pelvic pain. They compared this treatment with estrogen-progestin pills and found GnHR antagonist a better regimen. They also observed a better quality of life in the patients using GnRH antagonists as compared to those using estrogen-progestin pills [13, 14].

Factors that are essential for the determination of an optimal treatment are its symptoms, localization, age of the patient, duration, recurrence, and activity. The major challenge of any type of treatment is the symptoms of the disease. The only combined therapy of hormone and surgical intervention is capable of treating complex stages of endometriosis and overcoming the symptoms.

CONCLUSION

The major objective of the treatment of endometriosis is ovarian downregulation which can be achieved by GnRH agonists. A combined treatment including hormonal therapy and surgical intervention is used in complex diseases. The three steps of the combined therapy are surgical laparoscopy, hormonal therapy for 3-6 months, and then a second-look laparoscopy. The efficacy of the combined therapy is better than exclusive surgical or hormonal therapy. The combined therapy has a higher cure rate, higher pregnancy rate, and a lesser recurrence rate.

Funding source: None

Conflict of interest: None

Permission: Permission was taken from the ethical review committee of all institutes

REFERENCES

1. Greene AD, Lang SA, Kendziorski JA, Sroga-Rios JM, Herzog TJ, Burns KA. Endometriosis: where are we and where are we going? Reproduction (Cambridge, England). 2016 Sep; 152(3): R63.
2. Sarria-Santamera A, Orazumbekova B, Terzic M, Issanov A, Chaowen C, Asúnsolo-del-Barco A. Systematic review and meta-analysis of incidence and prevalence of endometriosis. Healthcare 2021 Jan (Vol. 9, No. 1, p. 29). Multidisciplinary Digital Publishing Institute.
3. Husain F, Siddiqui ZA, Siddiqui M. A case of endometriosis presenting as an inguinal hernia. Case Reports. 2015 Mar 11; 2015:bcr2014208099.
4. Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vanderkerchove P. Ovulation suppression for endometriosis for women with subfertility. Cochrane Database of Systematic Reviews. 2007(3).
5. Davis LJ, Kennedy SS, Moore J, Prentice A. Oral contraceptives for pain associated with endometriosis. Cochrane Database of Systematic Reviews. 2007(3).
6. Ferrero S, Camerini G, Seracchioli R, Ragni N, Venturini PL, Remorgida V. Letrozole combined with norethisterone acetate compared with norethisterone acetate alone in the treatment of pain symptoms caused by endometriosis. Human Reproduction. 2009 Dec 1; 24(12):3033-41.
7. Schrager SB, Falleroni J, Edgoose J. Evaluation and treatment of endometriosis. American family physician. 2013 Jan 15; 87(2):107-13.
8. Guo SW. Recurrence of endometriosis and its control. Human reproduction update. 2009 Jul 1; 15(4):441-61.
9. Rezende GP, Venturini MC, Kawagoe LN, Gomes DA, Benetti-Pinto CL. Surgery versus hormone-based treatment for pain control in deep infiltrating endometriosis: a retrospective cohort study. Current Medical Research and Opinion. 2022 Jan 21(just-accepted):1-1.
10. Alkatout İ, Meinhold-Heerlein I, Keckstein J, Mettler L. Endometriosis: A concise practical guide to current diagnosis and treatment. Journal of the Turkish German Gynecological Association. 2018 Sep; 19(3):173.
11. Opoku-Anane J, Tyan P, Klebanoff JS, Clay J, Moawad GN. Postoperative Hormonal Suppression for Prevention of Deeply Infiltrative Endometriosis Recurrence after Surgery. Current Obstetrics and Gynecology Reports. 2018 Sep; 7(3):133-8.
12. Schweppe KW, Ebert AD. Haben orale Kontrazeptiva einen Stellenwert für die Prophylaxe und Therapie der Endometriose? Geburtshilfe und Frauenheilkunde. 2020 Jul; 80(07):672-4.
13. Regidor PA, Regidor M, Schmidt M, Ruwe B, Lübben G, Förtig P, Kienle E, Schindler AE. A prospective randomized study comparing the GnRH-agonist leuprorelin acetate and the gestagen lynestrenol in the treatment of severe endometriosis. Gynecological endocrinology. 2001 Jan 1; 15(3):202-9.
14. Zupi E, Lazzeri L, Exacoustos C. Medical and Surgical Management of Endometriosis. How to Perform Ultrasonography in Endometriosis 2018 (pp. 13-26). Springer, Cham.