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Original Article

Effects of Leuprorelin Acetate Combined with Reverse Addition Therapy on Sex Hormone Levels in Patients with Ovarian Endometriosis Cyst

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ABSTRACT

Objectives: This study aimed to assess the effects of leuprorelin acetate combined with reverse addition therapy on the sex hormone levels in patients with ovarian endometriosis cyst. **Materials and Methods:** A total of 91 patients with ovarian endometriosis cyst admitted from April 2021 to April 2022 were divided into a control group (n=45) and a research group (n=46) according to the treatment regimens they received during clinical management. The control group was given leuprorelin acetate treatment, based on which reverse addition therapy was combined in the research group. **Results:** After treatment, the levels of serum Human Epididymis Protein 4 (HE4), Carbohydrate Antigen 125 (CA125), Anti-Mullerian hormone (AMH), estradiol (E_2), Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), High-Mobility Group Box 1 (HMGB1) and Retinol-Binding Protein 4 (RBP4) declined, while the Antral Follicle Count (AFC) rose in both groups, and the improvement was greater in the research group than that in the control group (p<0.05). The research group had higher clinical response and menstrual cycle recovery rates and lower cyst recurrence rate than those of the control group (p<0.05). **Conclusion:** Leuprorelin acetate combined with reverse addition therapy reduces the cyst recurrence rate probably by inhibiting the expression of AMH and regulating the levels of HE4, CA125, HMGB1 and RBP4.

Keywords: Endometriosis, Ovarian, Leuprolide, Ovarian Cysts, Sex Hormones.

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INTRODUCTION

Endometriosis is a common gynecological disease among women of reproductive age, characterized by the presence and cyclical bleeding of endometrial tissue outside the uterine cavity. It often manifests as dysmenorrhea, chronic pelvic pain, infertility, and, in some cases, malignant transformation.[1] The disease imposes a substantial burden on women's physical and mental health, leading to impaired quality of life and reduced fertility potential. Recent epidemiological studies have indicated that both the incidence and recurrence rates of endometriosis have been increasing annually, making it an important global reproductive health issue.[2]

Ovarian endometriosis cyst, also known as ovarian endometrioma, is the most common subtype of endometriosis. It exhibits biological behaviors resembling malignancy, such as invasion, implantation, and recurrence, which may lead to severe pelvic adhesions and damage to adjacent tissues.[3] Because of its chronic and relapsing nature, ovarian endometriosis cyst remains a major cause of pelvic pain and infertility in women of childbearing age.

Currently, laparoscopic cystectomy is considered the preferred surgical option for preserving ovarian function and alleviating symptoms.[4] However, surgical excision may inadvertently damage ovarian tissue and reduce ovarian reserve. Therefore, postoperative adjuvant hormonal therapy is often required to suppress residual ectopic endometrial activity and prevent recurrence. Leuprorelin acetate, a Gonadotropin-Releasing Hormone (GnRH) agonist, has been widely used for this purpose. It effectively alleviates endometriosis-related symptoms by inhibiting pituitary gonadotropin secretion and reducing circulating estrogen levels.[5,6] Nevertheless, prolonged administration may lead to hypoestrogenic adverse effects such as vasomotor symptoms and bone mineral loss.

To mitigate these limitations, the addition of low-dose estrogen and progestin, known as reverse addition or add-back therapy, has been introduced to maintain estrogen within a physiological threshold and thereby improve tolerability while maintaining

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therapeutic efficacy.[7] Despite its increasing clinical use, there is a lack of evidence on how reverse addition therapy influences sex hormone profiles and ovarian reserve in patients undergoing leuprorelin treatment. Clarifying these effects is of great clinical significance for optimizing individualized hormonal management and improving reproductive outcomes. Therefore, this study aimed to evaluate the effects of leuprorelin acetate combined with reverse addition therapy on sex hormone levels and ovarian function in patients with ovarian endometriosis cyst.

MATERIALS AND METHODS

General data

The sample size was primarily determined according to the number of eligible patients who met the inclusion and exclusion criteria during the study period. Because the study was based on a defined patient population from our hospital database, a convenience sampling approach was applied. To ensure the adequacy of statistical power, a *post hoc* power analysis was performed based on the primary outcome indicators. The analysis indicated that the current sample size provided a power greater than 0.8 to detect significant between-group differences at a two-sided α level of 0.05, confirming that the sample size was sufficient for the study objectives. A total of 91 patients with ovarian endometriosis cyst admitted to our hospital from April 2021 to April 2022, patients were assigned to the control or research group according to the treatment regimens they received during clinical management. A total of 102 patients were initially identified. After excluding those with incomplete clinical data (n=5), previous hormonal therapy within 3 months (n=3), and other gynecological malignancies (n=3), 91 eligible patients were finally included in the study. Among them, 45 patients received leuprorelin acetate alone (control group), and 46 received leuprorelin acetate combined with reverse addition therapy (research group).

The inclusion criteria were defined as follows: 1) Patients meeting the diagnostic criteria for ovarian endometriosis cyst in the *Standard for Diagnosis and Treatment of* Endometriosis,[8] 2) those with an age 20 years old, 3) those with single-vessel disease, 4) those with fertility desire, 5) those with a regular previous menstrual cycle of 21-35 d, 6) those with a cystic mass in a diameter ≥4 cm within the region of unilateral uterine adnexa as shown in ultrasound, computed tomography or magnetic resonance imaging, 7) those diagnosed pathologically after operation, and 8) those who signed the informed consent.

The exclusion criteria were set as follows: 1) Patients suffering from the recurrence of ovarian endometriosis cyst, 2) those with hysteromyoma or adenomyosis, 3) those who had pelvic inflammatory diseases, 4) those with autoimmune disease or metabolic bone disease, 5) those who previously received ovarian surgery, 6) those suffering from congenital adrenal hyperplasia or androgen-secreting tumor, 7) those with a malignant tumor, or 8) those who were allergic or highly sensitive to the drugs used in this study.

Methods

Both groups received laparoscopic surgery, which was successfully completed. In the control group, leuprorelin acetate was given as follows. Leuprorelin acetate sustained-release microspheres were subcutaneously injected at 2-3 d after the first postoperative menstruation at 28 d/time as a course of treatment for 6 courses.

Research group: On the basis of the procedures in the control group, reverse addition therapy was combined. Since the first injection of leuprorelin acetate, estradiol valerate at 1 mg/time, 1 time/d and medroxyprogesterone acetate tablets at 6 mg/time, 1 time/d were taken until the end of treatment.

Determination of levels of epididymis protein 4 (HE4), Carbohydrate Antigen 125 (CA125), High-Mobility group box 1 (HMGB1) and Retinol Binding Protein 4 (RBP4)

A total of 5 mL of fasting peripheral venous blood was harvested from each patient in the two groups and subjected to high-speed centrifugation for 15 min. Then the resulting sample was left to stand and the supernatant was isolated for detection. The levels of HE4, CA125, HMGB1 and RBP4 were measured by enzyme-linked immunosorbent assay using commercial kits (Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai, China). 5 mL of fasting venous blood was drawn, left to stand at room temperature and centrifuged at a high speed, and the supernatant was isolated. With blank wells, standard wells and sample-to-be-tested wells set in a microplate reader, the sample diluent, the standard solution and the sample to be tested were added, respectively, mixed well and covered with films, followed by incubation for 60 min. Then the liquid in the wells was discarded and spun dry, and the reaction plate was washed. A total of 100 μL of HE4, CA125, HMGB1, and RBP4 detection solution was added, covered with films, and incubated for 60 min. After the liquid in the wells was discarded and spun dry, the reaction plate was washed and added with 100 μL of substrate solution, followed by color development in the dark for 0.5 hr. The reaction was terminated by adding stop buffer and flicking the microplate reader. Finally, the absorbance value was measured at 450 nm by a highly qualified laboratory doctor using a microplate reader (iMarck, Bio-Rad, USA) strictly according to the operating instructions of the reagents. An evaluation was performed on the day of enrollment and after treatment.

Detection of ovarian reserve function

The level of serum Anti-Mullerian Hormone (AMH) was measured by a Cabra2905 electrochemical luminescence phase analyzer (Roche Diagnostics, Mannheim, Germany). The reagents were added in sequence for reaction by a highly qualified laboratory doctor strictly following the operating instructions of

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the reagents. The Antral Follicle Count (AFC) was measured by a color Doppler ultrasound device. An evaluation was performed on the day of enrollment and after treatment.

Detection of sex hormone levels

The levels of Estradiol (E_2), Luteinizing Hormone (LH), and Follicle-Stimulating Hormone (FSH) were measured using an automatic biochemical analyzer (AU5800, Beckman Coulter, USA) and matched reagent kits (Beckman Coulter, USA). An evaluation was performed on the day of enrollment and after treatment.

Assessment of treatment outcomes

Marked response was defined when clinical symptoms, pelvic tenderness nodules and sense of tenderness disappeared. Moderate response was confirmed in the patients with relieved abdominal pain, dysmenorrhea and other symptoms, as well as sense of tenderness and reduced pelvic tenderness nodules. No improvement and even worsening of clinical symptoms indicated no response.

Observation of menstrual cycle recovery and cyst recurrence

The menstrual cycle recovery and cyst recurrence were recorded in the two groups during the treatment. Chocolate cysts >2 cm in diameter found by gynecological and ultrasound examinations were defined as recurrence.

Statistical analysis

SPSS 20.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The normality of continuous variables was tested using the Shapiro-Wilk test. Measurement data were presented as mean±deviation ($\bar{x}\pm s$). Comparisons between groups were performed using the independent-samples *t*-test, while within-group comparisons before and after treatment were conducted using the paired *t*-test. Count data were expressed as percentage (%) and compared between the two groups by the χ^2 test. $p<0.05$ denoted that the differences were statistically significant.

RESULTS

Baseline clinical data

There were no significant differences in the general baseline characteristics between the two groups ($p>0.05$), indicating good comparability. The control group included 45 patients and the research group included 46 patients. The mean age was (27.50±3.83) years in the control group and (27.50±6.38) years in the research group. The mean course of disease was (3.20±0.22) months and (3.38±0.65) months, respectively. The mean body mass index was (22.51±1.22) kg/m² and (22.14±1.08) kg/m², and the mean cyst diameter was (5.32±0.40) cm and (5.40±0.36) cm, respectively. The lesion site (left/right) was 20/25 in the control group and 23/23 in the research group. Statistical analysis showed no significant differences between the two groups in any of these variables (t or χ^2 values: 1.727, 1.533, 1.003, 0.282; all $p>0.05$).

Levels of serum HE4 and CA125

No significant differences were observed between the two groups in the levels of serum HE4 and CA125 before treatment ($p>0.05$). After treatment, the research group had lower levels of serum HE4 and CA125 than those of the control group ($p<0.05$) (Table 1).

Ovarian reserve function

There was no significant difference between the two groups in the ovarian reserve function before treatment ($p>0.05$). After treatment, the level of AMH decreased, but AFC increased in the two groups. The improvement of the ovarian reserve function in the research group was better than that of the control group ($p<0.05$) (Table 2).

Levels of sex hormones

No significant differences were observed between the two groups in the levels of sex hormones before treatment ($p>0.05$). After treatment, the research group had lower levels of E_2, LH and FSH than those of the control group ($p<0.05$) (Table 3).

Levels of serum HMGB1 and RBP4

No significant differences were observed between the two groups in the levels of serum HMGB1 and RBP4 before treatment

Table 1: Levels of serum HE4 and CA125 ($\bar{x}\pm s$).

Group	*n*	HE4 (U/L)		CA125 (IU/mL)	
		Before treatment	After treatment	Before treatment	After treatment
Control	45	9.94±3.21	8.52±2.12	75.44±3.24	44.59±2.78
Research	46	9.81±3.03	7.20±2.02	75.30±3.08	21.18±1.84
t		0.199	3.041	0.211	47.470
p		0.843	0.003	0.833	0.001

HE4: Human Epididymis Protein 4; CA125: Carbohydrate Antigen 125; Data are expressed as mean±SD. Comparisons between groups were performed using the independent-samples t-test; $p<0.05$ was considered statistically significant.

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(p>0.05). After treatment, the research group had lower levels of serum HMGB1 and RBP4 than those of the control group (p<0.05) (Table 4).

Treatment outcomes

In terms of treatment efficacy, the overall clinical response rate in the research group was significantly higher than that in the control group (p<0.05). In the control group (n=45), 17 patients (37.78%) showed a marked response, 19 (42.22%) had a moderate response, and 9 (20.00%) showed no response, resulting in an overall response rate of 80.00%. In the research group (n=46), 27 patients (58.70%) showed a marked response, 17 (36.96%) had a moderate response, and 2 (4.35%) showed no response, yielding an overall response rate of 95.65%. Statistical analysis revealed that the difference in overall response rates between the two groups was significant (χ^2=5.244, p=0.022).

Menstrual cycle recovery and cyst recurrence

Regarding menstrual cycle recovery and cyst recurrence, the research group demonstrated better outcomes than the control group (p<0.05). In the control group (n=45), 30 patients (66.67%) showed menstrual cycle recovery, and 7 (15.56%) experienced cyst recurrence. In the research group (n=46), 41 patients (89.13%) achieved menstrual cycle recovery, and only 1 (2.17%) had cyst recurrence. The differences between the two groups were statistically significant for both menstrual cycle recovery (χ^2=6.694, p=0.010) and cyst recurrence (χ^2=5.080, p=0.024).

DISCUSSION

This study investigated the effects of leuprorelin acetate combined with reverse addition therapy on sex hormone levels in patients with ovarian endometriosis cyst. The results showed that the combined therapy more effectively reduced serum HE4, CA125, AMH, HMGB1 and RBP4 levels, improved ovarian reserve function, and promoted menstrual cycle recovery compared

Table 2: Ovarian reserve function ($\bar{x}$±s).

Group	*n*	AMH (μg/L)		AFC (n)	
		Before treatment	After treatment	Before treatment	After treatment
Control	45	5.30±1.14	4.32±0.68	4.14±0.63	4.68±0.71
Research	46	5.07±1.00	3.13±0.39	4.10±0.58	5.84±0.85
t		1.024	10.270	0.315	7.058
p		0.309	0.001	0.753	0.001

AMH: Anti-Müllerian Hormone; AFC: Antral Follicle Count; Data are expressed as mean±SD. Comparisons between groups were performed using the independent-samples t-test; p<0.05 was considered statistically significant.

Table 3: Levels of sex hormones ($\bar{x}$±s).

Group	*n*	E_2 (pmol/L)		LH (U/L)		FSH (U/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	45	220.55±23.75	106.87±13.68	6.54±1.40	3.05±1.23	14.44±2.65	8.23±1.35
Research	46	220.04±22.98	58.25±6.63	6.43±1.38	2.14±0.88	14.57±2.84	5.15±1.04
t		0.104	21.650	0.686	4.066	0.226	12.210
p		0.917	0.001	0.494	0.001	0.822	0.001

E2: Estradiol; LH: Luteinizing Hormone; FSH: Follicle-Stimulating Hormone; Data are expressed as Mean±SD. Comparisons between groups were performed using the independent-samples t-test; p<0.05 was considered statistically significant.

Table 4: Levels of serum HMGB1 and RBP4 ($\bar{x}$±s), μg/L).

Group	*n*	HMGB1		RBP4	
		Before treatment	After treatment	Before treatment	After treatment
Control	45	52.34±11.08	42.10±7.16	22.08±1.80	16.63±0.49
Research	46	51.76±10.94	30.26±7.40	21.76±1.93	14.49±0.50
t		0.251	7.754	0.818	20.620
p		0.802	0.001	0.416	0.001

HMGB1: High-Mobility Group Box 1; RBP4: Retinol-Binding Protein 4; Data are expressed as mean±SD. Comparisons between groups were performed using the independent-samples *t*-test; p<0.05 was considered statistically significant.

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with leuprorelin acetate alone. These findings indicate that the combination therapy has superior clinical efficacy and may reduce cyst recurrence.

Ovarian endometriosis cyst, a common gynecological estrogen-dependent disease, is mainly manifested as dysmenorrhea, infertility, pelvic pain and other symptoms, and has malignant biological behaviors such as invasion, metastasis and recurrence, thereby threatening patients' activities of daily living and quality of life.[9-12] Studies have shown that long-term damage to the endometrial glands causes serious pelvic adhesions and blurred lesions in the adjacent tissue boundaries. If surgical treatment is adopted alone, it will be difficult to effectively remove the lesions, thus heightening the risk of postoperative recurrence.[13,14] As a gonadotropin-releasing hormone high-activity analogue, leuprorelin acetate has been found through pharmacological studies to be widely used to treat or relieve endometriosis since it can alleviate symptoms of endometriosis and other sex hormone-dependent diseases by preventing the pituitary from secreting gonadotropin.[15,16] According to studies, while relieving the pain to the largest extent, leuprorelin acetate can reduce serum estrogen content, improve the microcirculation around the lesion, accelerate the atrophy and degeneration of the endometrium, and alleviate the symptoms in the treatment of endometriosis.[16,17] Reverse addition therapy advocates that estrogen should be controlled within the theoretical threshold range to effectively inhibit ectopic endometrial growth without affecting estimated metabolism.[18] Studies have established that the long-term application of leuprorelin acetate has a limitation of hormone dependence with recurrent symptoms due to drug withdrawal, which brings difficulties to the treatment of the disease, so that reverse addition therapy is widely used in clinics. The results of this study showed that the research group was superior to the control group in the changes in the levels of HE4, CA125, AMH, HMGB1 and RBP4, suggesting that leuprorelin acetate combined with reverse addition therapy has good clinical efficacy in the treatment of patients with ovarian endometriosis cyst. The possible reason is that the combined treatment scheme exerted different degrees of inhibitory effects on the hypothalamic-pituitary-ovarian gonadal axis function, thereby shrinking the ectopic lesions, inhibiting the ovulation effect, and reducing the serum estrogen content to the greatest extent. Moreover, it ameliorates the microcirculation around the ectopic lesions, and accelerates endometrial tissue repair while relieving pain.

According to the results of this study, the levels of E_2, LH and FSH in the two groups decreased after treatment, showing better efficacy in the research group. It is considered that leuprorelin acetate combined with reverse addition therapy has a positive effect on the improvement of sex hormone levels in patients with ovarian endometriosis cyst. E_2 is a natural estrogen secreted by mature ovarian follicles, which is a predictor for the ovarian reserve function.[19] LH can regulate the development and excretion of follicles by promoting the synthesis and secretion of steroid hormones, thereby interacting with FSH.[20] FSH, as a glycoprotein secreted by the anterior pituitary gland, can make small follicles enter the stage of hierarchical development b.[21] The results of this study showed that the levels of E_2, LH and FSH in the research group were lower than those in the control group, suggesting that leuprorelin acetate combined with reverse addition therapy is of great significance for ameliorating the levels of sex hormones in patients with ovarian endometriosis cyst, regulating the endocrine system and enhancing ovarian function suppression, which effectively improves the efficacy.

Our findings are consistent with recent studies showing that the use of Gonadotropin-Releasing Hormone (GnRH) agonists before or after conservative surgery effectively suppresses ovarian estrogen production and improves postoperative outcomes.[22] Similar evidence indicates that prolonged-release formulations of leuprorelin acetate provide stable hormone suppression, reduce recurrence rates, and improve pain control.[23] Moreover, recent evidence indicates that postoperative hormonal suppression (e.g., GnRH agonists or dienogest) improves fertility outcomes and is generally well tolerated after conservative surgery,[24] supporting the benefit of integrated medical therapy in disease control. The reduction of LH and FSH levels observed in this study further supports that combined therapy can modulate the hypothalamic-pituitary-ovarian axis more effectively than leuprorelin alone. This coordinated inhibition reduces gonadotropin stimulation, suppresses follicular development, and maintains a low-estrogen environment that inhibits ectopic endometrial proliferation. Recent pharmacological reviews have confirmed that leuprorelin acetate alleviates endometriosis-related symptoms mainly by suppressing pituitary gonadotropin release and reducing systemic estrogen levels, thereby decreasing lesion activity and pain, consistent with our findings.[25]

This study has several limitations that should be acknowledged. First, the sample size was relatively small and derived from a single center, which may limit the generalizability of the findings. Second, the follow-up period was short, and long-term outcomes such as recurrence rate and reproductive prognosis were not fully evaluated. Third, the study did not include detailed assessment of patient-reported outcomes or hormonal changes over extended treatment intervals, which could provide additional insight into therapeutic efficacy and tolerability. Therefore, further multicenter studies with larger cohorts and longer follow-up are warranted to validate and expand upon these results.

CONCLUSION

In conclusion, leuprorelin acetate combined with reverse addition therapy plays a positive role in improving the sex hormones of patients with ovarian endometriosis cyst, promotes their menstrual cycle recovery and lowers the cyst recurrence rate

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probably by inhibiting the expression of AMH and regulating the levels of HE4, CA125, HMGB1 and RBP4.

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ABBREVIATIONS

AMH: Anti-Müllerian Hormone; **AFC:** Antral Follicle Count; **CA125:** Carbohydrate Antigen 125; **E2:** Estradiol; **FSH:** Follicle-Stimulating Hormone; **GnRH:** Gonadotropin-Releasing Hormone; **HE4:** Human Epididymis Protein 4; **HMGB1:** High-Mobility Group Box 1; **LH:** Luteinizing Hormone; **RBP4:** Retinol-Binding Protein 4.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHORS CONTRIBUTIONS

Conceptualization, X.L.L. and B.L.; Methodology, Z.R.D.; Software, H.M.L.; Validation, X.L.L. and B.L.; Formal Analysis, X.L.L.; Investigation, H.M.L.; Resources, Z.R.D.; Data Curation, X.L.L.; Writing – Original Draft Preparation, H.M.L.; Writing – Review & Editing, X.L.L. and B.L.; Visualization, Z.R.D.; Supervision, X.L.L. and B.L.; Project Administration, X.L.L. and B.L.; Funding Acquisition, B.L.

SUMMARY

This study evaluated the clinical efficacy of leuprorelin acetate combined with reverse addition therapy in patients with ovarian endometriosis cyst. A total of 91 patients were assigned to the control and research groups based on their respective treatment plans. Both groups underwent laparoscopic surgery, with the research group receiving additional reverse addition therapy. Compared with leuprorelin acetate alone, the combination therapy more significantly reduced levels of serum HE4, CA125, AMH, HMGB1, and RBP4, improved sex hormone profiles (E2, LH, FSH), increased Antral Follicle Count (AFC), and achieved higher clinical response rates. Moreover, the research group exhibited better menstrual cycle recovery and a lower cyst recurrence rate. These findings suggest that reverse addition therapy enhances the therapeutic effect of leuprorelin acetate by improving endocrine function and reducing recurrence risk in patients with ovarian endometriosis cyst.

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