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Effect of Mirena intrauterine device combined with GNRH-A on endometriosis, sex hormone level and carbohydrate antigen 125

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ABSTRACT

To investigate the clinical value of Mirena (levonorgestrel intrauterine sustained release system) combined with gonadotropin-releasing hormone agonist (GnRH-a) in patients with endometriosis, 80 patients with endometriosis (March 2019 ~ March 2020) were selected as the research object. According to the "random number table method", they were divided into the control group (treated with GnRH-a) and the observation group (treated with Mirena IUD combined with GnRH-a), with 40 cases included in each group. The total clinical efficacy, sex hormone level, carbohydrate antigen 125 (CA125) level, degree of pain and recurrence rate indexes were compared between the two groups. Results showed that the total effective rate of 92.50% in the observation group was higher than 75.00% in the control group ($P < 0.05$). Intercourse pain of dysmenorrhea and sexual intercourse pain (VAS) in the two groups were compared before treatment. After treatment, the VAS scores in the two groups decreased, and the VAS scores in the observation group were lower than those in the control group ($P<0.05$). The levels of E2, FSH, LH and CA125 in the observation group were lower than in the control group ($P<0.05$). The recurrence rate of 5.00% in the observation group was lower than 20.00% in the control group ($P<0.05$). In conclusion, Mirena IUD combined with GnRH-a can improve the clinical efficacy of endometriosis, improve ovarian function, effectively regulate serum factors, further alleviate the symptoms of sexual intercourse pain and dysmenorrhea, control the risk of postoperative recurrence and achieve an ideal therapeutic effect.

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Introduction

Endometriosis, as one of the common and high incidence gynecological diseases in clinics, is a local lesion caused by the appearance of endometrial tissue outside the uterine cavity, which has the behavioral characteristics of invasion, implantation and other similar to the malignant tumor. The disease is more common in women aged 20-45 years, the incidence of women of childbearing age is as high as 10%, after the onset of the disease, most of the manifestations are pain during intercourse, dysmenorrhea, infertility and other situations, causing a serious impact on women's physical and mental health, and lead to a great decline in their quality of life(1-3). The main clinical treatment methods for the disease are surgery and drugs. Surgical treatment can effectively remove the lesions to a certain extent, but there is a certain risk of recurrence in the later stage. However, the recurrence rate after simple drug treatment is greater, so it is necessary to seek more effective and safe treatment. Gnrh-a can inhibit gonadotropin and maintain a low level of gonadotropin. Mirena intrauterine sustained release system can slowly release highly effective progesterone, effectively inhibit endometrial growth, maintain stable endometrial function, control hormone secretion, and effectively relieve patients' pain (4,5). The combined use of the two can make lesions atrophy, effectively inhibiting the recurrence of the disease after surgery (6-8). In order to evaluate the clinical value of Mirena IUD combined with GNRH-A, a comparative study was conducted on 80 patients with endometriosis (From March 2019 to March 2020).

Materials and Methods

General Information

Eighty cases of endometriosis were studied.

Inclusion criteria included: ① Consistent with the diagnostic criteria of endometriosis established by the World Health Organization, and confirmed by ultrasound examination. ② Hysteroscopic conservative surgery was performed, and pathological diagnosis was confirmed as endometriosis stage iii and iv, and there was no need for fertility temporarily. ③ The medical records were reliable and complete. ④ No related drug contraindications. ⑤ Patients voluntarily participated in the follow-up.

Exclusion criteria included: ① lack of consciousness, serious mental disorder. ② Recent history of infection. ③ Complicated with malignant tumor. ④ Serious diseases of liver and kidney and other major organs. ⑤ Take drugs that affect sex hormone levels within half a year. ⑥ The coagulation mechanism is abnormal. The study was approved by the hospital's medical ethics Committee with informed consent and signed documents.

According to the "random number table method", all subjects were divided into two groups -- control group and the observation group (n=40 cases). General data of patients Control group: 20-39 years old, average (31.63±3.05) years old. The duration of the disease was 1-3 years, with

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an average duration of (2.16±0.41) years. Observation group: aged 21-40 years old, average (31.87±3.58) years old. The duration of the disease ranged from 1 to 4 years, with an average duration of (2.76±0.58) years. There was no significant difference in baseline data between the two groups (P > 0.05).

Methods

Control group: GnRH-A was treated with a subcutaneous injection of 3.75mg on the 1st to 5th day of menses, once every 28 days, for 3 consecutive times.

Observation group: On the basis of the control group, Mirena intrauterine device was combined with the control group. During the third injection of GNRH-A, patients were instructed to take the bladder stone position, clean the cervix and vagina, and the anterior cervix lip was clamped with cervical forceps and fixed on the uterus. When we put a man on, effective fixation with forceps and slight pull the opposite direction, the cervix tube uterine sound, clear the cervical depth, placement, month, determine the distance between cervical 2 cm, pull the slider, after 5 to 10 s, push placer to position the blocks, slide block drop-down, tail filament release, exit the placer, tail wire cut short, 2 cm distance from the opening of the cervix.

Observation indicators

① Determination of clinical efficacy: pelvic mass disappeared after ultrasound examination, and clinical symptoms disappeared completely, indicating significant effect; Pelvic mass disappeared after ultrasound examination, compared with the clinical symptoms significantly improved before treatment, it is effective. It is invalid if it does not meet the above standards.Response rate = (significant effect + effective)/number of cases ×100%.

② The patients were followed up for 1 year, and the degree of chronic pelvic pain, pain during intercourse, and dysmenorrhea were evaluated by the Visual Analogue Scale/Score (VAS). The total score was 10 points, 0 points for no pain, and 10 points for severe pain unbearable. A score of 1-3, 4-6, and 7-10 indicate mild, moderate, and severe pain(9).

③ Serum indicators: Venous blood was collected from all included patients, and centrifugation was carried out at 3000r/min speed for 10min. Serum samples were obtained and stored at -80C. Chemiluminescence was used to measure the following hormone levels: Estradiol (E2), Luteinizing hormone (LH) and Follicle Stimulating hormone (FSH) detection reagents were provided by Beijing Huadu Zhongsei Science and Technology Development Co., LTD. Automatic chemiluminescence analyzer was selected for detection. Serum Carbohydrate antigen 125 (CA125) level was measured simultaneously (10).

④ After 1-year follow-up, if patients relapse, determine the standards for: again cyclical, progressive abdominal pain and other clinical manifestations, visible in the pelvic cyst by ultrasonic examination (11).

Statistical methods

SPSS 23.0 statistical software was used for data analysis. Counting data were expressed as [N (%)], and measurement mean were expressed as (x±s). χ^2 and T-test were used and $P < 0.05$ was considered statistically significant.

Results

Comparison of total clinical response rate

The total effective rate of 92.50% in the observation group was significantly higher than 75.00% in the control group (P < 0.05); (Table 1).

Comparison of pain degree

Before treatment, there was no significant difference in the scores of chronic pelvic pain, dysmenorrhea and pain during intercourse (VAS) between the 2 groups (P>0.05). After treatment, VAS scores in the 2 groups were significantly decreased, and VAS scores in the observation group were significantly lower than those in the control group (P < 0.05); (Table 2).

Comparison of sex hormone levels

The levels of E2, FSH and LH in the two groups before treatment were compared (P > 0.05). After treatment, the levels of E2, FSH and LH in the observation group were lower than those in the control group (P < 0.05); (Table 3).

Comparison of ca125 levels

The level of CA125 in the observation group was significantly lower than that in the control group after treatment (P < 0.05); (Table 4).

Comparison of recurrence rates

The recurrence rate of the observation group (5.00%) was significantly lower than that of the control group (20.00%) after a one-year follow-up (P < 0.05); (Table 5).

Table 1. Comparison of total clinical effective rate [N /%].

group	*n*	*	Effective	Invalid	Total effective rate (%)
Control	40	17 (42.50)	13 (32.50)	10 (25.00)	30 (75.00)
Observation	40	21 (52.50)	16 (40.00)	3 (7.50)	37 (92.50)
χ^2value	-		-		4.500
P-values	-		-		0.033

Table 2. Comparison of pain degree.

Group	*n*	Before the treatment	3 months after treatment	6 months after treatment	1 year after treatment
Control	40	5.36 ±1.66	1.72 ±0.45	1.84 ± 0.55	2.51± 0.68
Observation	40	5.45 ± 1.49	1.03± 0.22	1.01± 0.29	1.68 ± 0.52
T value	-	0.225	8.712	8.442	6.132
P values	-	0.799	< 0.001	< 0.001	< 0.001

Table 3. Comparison of E2, FSH and LH indicators.

Group	*n*	E2 (pmol/L)		FSH (IU/L)		LH (IU/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	40	71.21 ±8.32	66.41±10.63	6.72±2.13	5.89 ±1.22	13.82±3.6	9.71±2.65
Observation	40	71.36 ±8.43	59.29±12.91	6.26±2.05	4.85 ±1.12	13.91±3.5	7.22±1.58
T value	-	0.080	2.692	0.984	3.971	0.112	5.104
P values	-	0.936	0.008	0.328	< 0.001	0.910	< 0.001

Table 4. Comparison of CA125 levels (pg/ml).

Group	*n*	Before the treatment	After treatment
Control	40	116.58 + / - 13.52	68.77 + / - 8.25
Observation	40	117.15 + / - 12.61	46.77 + / - 7.22
T value	-	0.194	12.691
P values	-	0.845	< 0.001

Table 5. Comparison of late recurrence rates [N /%].

Group	*n*	Review the number of cases	Review rate (%)
Control	40	8	20.00
Observation	40	2	5.00
χ^2value	-	2.314	
P values	-	0.128	

Discussion

Endometriosis refers to the presence of endometrium tissue outside the uterine cavity caused by local lesions, its occurrence and endometrium species, blood countercurrent, body cavity metaplasia and so on. There is a certain relationship (12-13). Surgery is one of the effective means for treating this disease, which can effectively remove the lesions and relieve the symptoms of patients. However, some patients need fertility, and the lesions have special anatomical characteristics, and they interlock with the tissues and organs in the abdominal cavity. Therefore, conservative surgical treatment can remove the lesions visible to the naked eye to a certain extent. However, the residual lesions after surgery may lead to the recurrence of the disease under the influence of the body's relevant hormones due to the characteristics of diffusion, infiltration and hyperplasia (14,15). Therefore, adjuvant drug therapy is needed after conservative surgery to enhance clinical efficacy and prevent disease recurrence.

GnRH-a is a pituitary-ovarian inhibitor that can effectively inhibit the secretion of pituitary gonadotropin, further inhibit the release of progesterone and estrogen in the ovary, reduce the amount of estrogen secretion, inactivate cells in the intima, reduce the rate of angiogenesis and effectively control the disease (16,17). Mirena IUD is a T-shaped intrauterine sustained release system containing progesterone, which can slowly release levonorgestrel and effectively inhibit cell proliferation and estrogen secretion when placed in the uterine cavity of patients. At the same time, it can promote the expression of fatty acid synthase and effectively treat diseases (18). Results of this study: the total effective rate of the observation group was 92.50% higher than 75.00% of the control group ($P < 0.05$). After treatment, the levels of E2, FSH, LH and CA125 in the 2 groups were decreased, and the levels of the above indexes in the observation group were better than those in the control group ($P < 0.05$). It is suggested that the combination of GNRH-A and Mirena IUD can play a synergistic role in the treatment of endometriosis, and the two can promote each other in the treatment of endometriosis, solve the problem of individual differences, enhance the clinical efficacy and prevent the recurrence of the disease. The analysis is as follows, GnRH - a belongs to a kind of synthetic peptide, ten of FSH, LH release play a role, can maintain estrogen levels, drug spayed play, to reduce the effect of estrogen stimulation, support lesions, and the drug can induce apoptosis of ectopic endometrium, in the adjuvant treatment of endometriosis, and play an important role in the prevention of disease relapse (19). However, the long-term application of GNRH-A is prone to pseudomenopause, resulting in decreased bone mineral density of patients, and there are individual differences among different patients. For some patients, the treatment effect is not ideal after simple application of GnRH-A, and adjusting the dosage and changing the frequency of medication is easy to affect the safety of the medication, so the auxiliary application of other drugs is needed. Mirena placed in the uterine cavity of patients, intrauterine endometrial intervention, without affecting the level of estrogen, can reduce the endometrial E2, progesterone receptors, make the endometrial gland atrophy, inhibit the endometrial growth, reduce the endometrial reaction activity, effectively relieve symptoms (20,21).

The results also showed that the dysmenorrhea and sexual pain (VAS) scores in the observation group were significantly lower than those in the control group ($P < 0.05$). The recurrence rate of the observation group (5.00%) was significantly lower than the control group (20.00%) ($P < 0.05$). GnRH-a can inhibit gonadotropin, resulting in a rapid decrease of FSH and LH levels in a short period, promoting ectopic endometrial degeneration and atrophy and necrosis of focal tissues, controlling endometrial growth and effectively treating diseases. The drug can inhibit neuronal membrane discharge, and improve patients hyperalgesia, so as to effectively relieve pain symptoms.

However, a single drug is easy to cause side effects, can not be used in large doses, and clinical efficacy is not ideal (22). The progesterone activity of the Mirena intrauterine device is high, which can promote the decidualization of endometriosis, reduce the estrogen receptor level of endometriosis lesions, and then make the lesions atrophy, inhibit the growth of endometriosis, promote the decrease of endometrial activity, effectively improve the menstrual volume and relieve pelvic pain symptoms (23,24). It can be seen that the combination of the above two drugs can promote lesion atrophy, effectively regulate serum factors, improve hormone levels, improve ovarian reserve function, improve patients' pain and improve prognosis.

In conclusion, for endometriosis patients with Mirena IUD combined with GNRH-A, it can effectively regulate serum factors, regulate the release of sex hormones, relieve patients' pain, effectively control the disease recurrence rate, and achieve an ideal therapeutic effect.

References

1. Ha JK, Choi CW, Kim HW, Kang DH, Park SB, Kim SJ, Hong JB. An extremely rare case of gastric subepithelial tumor: gastric endometriosis. Clin Endosc. 2015 Jan;48(1):74-7. doi: 10.5946/ce.2015.48.1.74. Epub 2015 Jan 31. PMID: 25674531; PMCID: PMC4323438.
2. Escudero-Lara A, Cabañero D, Maldonado R. Surgical Induction of Endometriosis in Female Mice. Bio Protoc. 2020 Sep 20;10(18):e3763. doi: 10.21769/BioProtoc.3763. PMID: 33659421; PMCID: PMC7842549.
3. Nawaz MM, Masood Y, Usmani AS, Basheer MI, Sheikh UN, Mir K. Renal endometriosis: A benign disease with malignant presentation. Urol Case Rep. 2022 May 7;43:102110. doi: 10.1016/j.eucr.2022.102110. PMID: 35586402; PMCID: PMC9108729.
4. Chen J, Wang H, Dong Z, Liu J, Qin Z, Bao M, Yu H, Zhang S, Zhang W, Qi C, Wu J. GnRH-a-Induced Perimenopausal Rat Modeling and Black Cohosh Preparations' Effect on Rat's Reproductive Endocrine. Front Endocrinol (Lausanne). 2021 Dec 24;12:683552. doi: 10.3389/fendo.2021.683552. PMID: 35002948; PMCID: PMC8739485.
5. He W, Li X, Adekunbi D, Liu Y, Long H, Wang L, Lyu Q, Kuang Y, O'Byrne KT. Hypothalamic effects of progesterone on regulation of the pulsatile and surge release of luteinising hormone in female rats. Sci Rep. 2017 Aug 14;7(1):8096. doi: 10.1038/s41598-017-08805-1. PMID: 28808344; PMCID: PMC5556103.
6. Li X, Zhu X, He S, Jiang Z, Li H, Tian X, Long W, Xue M, Deng X, Ye M. High-intensity focused ultrasound in the management of adenomyosis: long-term results from a single center. Int J Hyperthermia. 2021;38(1):241-247. doi: 10.1080/02656736.2021.1886347. PMID: 33602049.
7. Chen X, Wu X, Zhu H. Acute urticaria as a side effect of the Mirena® (levonorgestrel-releasing intrauterine system): a case report. BMC Res Notes. 2014 Apr 3;7:209. doi: 10.1186/1756-0500-7-209. PMID: 24708811; PMCID: PMC3992142.
8. Zhang L, Yang H, Zhang X, Chen Z. [Efficacy and adverse effects of levonorgestrel-releasing intrauterine system in treatment of adenomyosis]. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2019 Apr 25;48(2):130-135. Chinese. doi: 10.3785/j.issn.1008-9292.2019.04.02. PMID: 31309749; PMCID: PMC8800644.
9. Song JH, Lu H, Zhang J, Li B. [Clinical study on the effectiveness and safety of combined laparoscopy and gonadotropin-releasing hormone agonist in the treatment of endometriosis]. Zhonghua Fu Chan Ke Za Zhi. 2013 Aug;48(8):584-8. Chinese. PMID: 24199923.
10. Xue H, Liu M, Hao W, Li Y. Clinical evaluation of laparoscopic surgery combined with triptorelin acetate in patients with endometriosis and infertility. Pak J Med Sci. 2018 Sep-Oct;34(5):1064-1069. doi: 10.12669/pjms.345.15574. PMID: 30344551; PMCID: PMC6191787.
11. Ahmady-Nezhad M, Rezainasab R, Khavandegar A, Rashidi S, Mohammad-Zadeh S. Perineal and right femoral hydatid cyst in a female with regional paresthesia: a rare case report. BMC Surg. 2022 Feb 23;22(1):64. doi: 10.1186/s12893-022-01516-z. PMID: 35197047; PMCID: PMC8867753.
12. Zhang J, Dong L, Zhang S, Wang L. Analysis of the clinical efficacy of leuprolide acetate in the treatment of obese patients with endometriosis and its role on the expression of MIF gene. Cell Mol Biol (Noisy-le-grand). 2022 Jan 2;67(4):282-288. doi: 10.14715/cmb/2021.67.4.31. PMID: 35809278.
13. Liang D, Zhang Y, Chen L, Shu L, He Y, Ma H, Qiao M, Wang N. The effect of ENEAS application in patients with endometriosis and its influence on the level of IL-8 and MCP-1. Cell Mol Biol (Noisy-le-grand). 2022 Jan 2;67(4):334-339. doi: 10.14715/cmb/2021.67.4.38. PMID: 35809271.
14. Ye MZ, Deng XL, Zhu XG, Xue M. [Clinical study of high intensity focused ultrasound ablation combined with GnRH-a and LNG-IUS for the treatment of adenomyosis]. Zhonghua Fu Chan Ke Za Zhi. 2016 Sep 25;51(9):643-649. Chinese. doi: 10.3760/cma.j.issn.0529-567X.2016.09.002. PMID: 27671043.
15. Yang XH, Ji F, AiLi A, TuerXun H, He Y, Ding Y. Effects of laparoscopic ovarian endometriosis cystectomy combined with postoperative GnRH-a therapy on ovarian reserve, pregnancy, and outcome recurrence. Clin Exp Obstet Gynecol. 2014;41(3):272-5. PMID: 24992774.
16. Chen J, Wang H, Dong Z, Liu J, Qin Z, Bao M, Yu H, Zhang S, Zhang W, Qi C, Wu J. GnRH-a-Induced Perimenopausal Rat Modeling and Black Cohosh Preparations' Effect on Rat's Reproductive Endocrine. Front Endocrinol (Lausanne). 2021 Dec 24;12:683552. doi: 10.3389/fendo.2021.683552. PMID: 35002948; PMCID: PMC8739485.
17. Gründker C, Emons G. Role of Gonadotropin-Releasing Hormone (GnRH) in Ovarian Cancer. Cells. 2021 Feb 18;10(2):437. doi: 10.3390/cells10020437. PMID: 33670761; PMCID: PMC7922220.
18. Starič KD, Taneska P, Zore A, Lukanović A, Kobal B, Cvjetićanin B, Jakopič K. Levonorgestrel-Releasing Intrauterine Contraceptive Device in the Peritoneal Cavity: A Report of Two Cases. J Reprod Med. 2017 Mar-Apr;62(3-4):215-17. PMID: 30230800.
19. Cao Y, Zhuang MF, Yang Y, Xie SW, Cui JG, Cao L, Zhang TT, Zhu Y. Preliminary study of quercetin affecting the hypothalamic-pituitary-gonadal axis on rat endometriosis model. Evid Based Complement Alternat Med. 2014;2014:781684. doi: 10.1155/2014/781684. Epub 2014 Oct 28. PMID: 25530789; PMCID: PMC4228827.
20. Yang XH, Ji F, AiLi A, TuerXun H, He Y, Ding Y. Effects of laparoscopic ovarian endometriosis cystectomy combined with postoperative GnRH-a therapy on ovarian reserve, pregnancy, and outcome recurrence. Clin Exp Obstet Gynecol. 2014;41(3):272-5. PMID: 24992774.
21. Lee KH, Jung YW, Song SY, Kang BH, Yang JB, Ko YB, Lee M, Han HY, Yoo HJ. Comparison of the efficacy of diegnogest and levonorgestrel-releasing intrauterine system after laparoscopic surgery for endometriosis. J Obstet Gynaecol Res. 2018 Sep;44(9):1779-1786. doi: 10.1111/jog.13703. Epub 2018 Jul 5. PMID: 29974633.
22. Chen J, Wang H, Dong Z, Liu J, Qin Z, Bao M, Yu H, Zhang S, Zhang W, Qi C, Wu J. GnRH-a-Induced Perimenopausal Rat Modeling and Black Cohosh Preparations' Effect on Rat's

Reproductive Endocrine. Front Endocrinol (Lausanne). 2021 Dec 24;12:683552. doi: 10.3389/fendo.2021.683552. PMID: 35002948; PMCID: PMC8739485.

23. Song SY, Lee SY, Kim HY, Park DB, Kim DE, Lee KH, Lee S, Yang JB, Yoo HJ. Long-term efficacy and feasibility of levonorgestrel-releasing intrauterine device use in patients with adenomyosis. Medicine (Baltimore). 2020 May 29;99(22):e20421. doi: 10.1097/MD.0000000000020421. PMID: 32481439.
24. Zhang S, Wang L, Zhang J, An W, Jia L. The efficacy and safety of Kuntai capsule combined with leuprorelin acetate in the treatment of endometriosis: A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2021 Mar 19;100(11):e25080. doi: 10.1097/MD.0000000000025080. PMID: 33725984; PMCID: PMC7982199.