



Short Communication

Clinical Effect of GnRH-a and Gestrinone after Severe Endometriosis Operation: Randomized Clinical Trial

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ABSTRACT

The objective of this study was to investigate the application effect of GnRH-a and gestrinone and nursing after severe endometriosis operation, looking at the long-term efficacy in preventing endometriosis recurrence and fertility outcomes. This study included 180 patients with severe endometriosis who were treated in our hospital. They were divided into the study group receiving GnRH-a treatment alone and the reference group receiving GnRH-a and gestrinone treatment. Patients in the reference group received routine nursing, while patients in the study group received comprehensive nursing intervention to compare the treatment outcomes of the two groups. Comparison of the two-year postoperative recurrence and pregnancy of the two groups showed no significant difference between the two groups, $p > 0.05$. Moreover, the incidence of adverse reactions in the two groups showed a relatively higher irregular uterine bleeding rate in the reference group than in the study group, $p < 0.05$. When compared to sole GnRH-a, this is the first trial to indicate that adding gestrinone to the GnRH-a regimen resulted in significantly less irregular uterine bleeding while maintaining the same long-term effectiveness in avoiding endometriosis recurrence and benefits for fertility outcomes.

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Authors' Contribution

JZ and YM collected the samples. JZ and LL analysed the data. YM and MW conducted the experiments and analysed the results. All authors discussed the results and wrote the manuscript.

Key words

Severe endometriosis, GnRH-a, Gestrinone

Endometriosis diseases include endometriosis and adenomyosis, both of which are caused by ectopic endometrium with growth function. Coexistence of the two is clinically possible. However, the pathogenesis and histology of the two are different, and differences also exist in clinical manifestations and sensitivity to ovarian hormones. The former is sensitive to progesterone and the latter is not sensitive. Epidemiological surveys show that childbearing age has high incidence of endometriosis, 76% of the disease attacked in 25-45-year-old age group (Xu, 2019; Cao, 2019; Hao, 2019), which coincided with the characteristics of endometriosis as a hormone dependent disease. It has been reported that the disease also attacked

women who have been treated with hormone supplementation after menopause.

For patients with severe endometriosis, to reduce the recurrence rate and increase the pregnancy rate, a drug-assisted treatment mode is usually adopted after surgery. Gonadotropin-releasing hormone agonists (GnRH-a) are relatively common, but are expensive and will lead to significant low estrogen symptoms. Gestrinone is also a drug commonly used in endometriosis, which can prevent the low estrogen side effects produced by long-term use of GnRH-a and is applicable for low- and middle-income patients (Ekerstad *et al.*, 2018; Surr *et al.*, 2018). As the possibility of GnRH-a application in endometriosis post-operation setting is being supported by valuable evidence of meta-analysis in literature (Zheng *et al.*, 2016) but its combination with Gestrinone is not well evaluated, relying on the well-known safety of both medications (Nieto *et al.*, 1997), we conducted this clinical trial. This study observed and analyzed the effects of GnRH-a, gestrinone, and nursing after severe endometriosis operation. As the literature suggests the possibility of recurrence of endometriosis in long term (Zheng *et al.* 2016), we aimed

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at evaluating our study outcomes in 2 years follow-ups.

Materials and methods

This was a prospective randomized clinical trial conducted at the Second Hospital of Jilin University, Changchun, 130041, China, from January 2016 to May 2021. Patients and their families had the right to know and signed a formal informed consent form. The study was initiated with the approval of the Hospital Ethics Association.

The study included 180 patients with severe endometriosis. Simple-available sampling was performed based on the census sampling method of all patients being operated on from January, 2016 to May, 2021. The inclusion criteria were all of the patients had stage III or IV endometriosis. The staging was determined according to the 1985 revised endometriosis staging criteria (r-AFS) of American Society of Fertility (Rørth *et al.*, 2018). Patients who did not refer for follow-ups were excluded. The patients were randomly divided into study and reference groups, with 90 patients in each giving a unique code to each patient and simple randomization of each group was conducted.

All patients received targeted surgical procedure based on the results of laparoscopy. Scissors or electric knives were used to remove the ovarian, sacrospinous ligament, peritoneum and uterine surface lesions. The small lesions were directly burned bipolarly for elimination. For patients with ovarian endometriotic cysts, separation of adhesions was performed and ovarian cystectomy was implemented, and bipolar electrocoagulation was used to stop bleeding. Methylene blue test was performed in case of infertility and salpingostomy was performed on those with blocked distal fallopian tube.

After the operation, the reference group was treated with GnRH-a alone, and the study group was treated with GnRH-a and gestrinone. In the first month after surgery, GnRH-a was applied during 2nd-5th days of menstruation. There were two courses of treatment, each lasted three months. The study group received GnRH-a treatment in the first and second courses of treatment. 3.75 mg was subcutaneously injected once every four weeks for six months. The reference group was treated with GnRH-a in the first treatment course of three months, which was switched to oral administration of gestrinone 2.5 mg in the second course, twice a week for three months.

The reference group only received general health education, preoperative examination, diet guidance, while the study group received comprehensive nursing intervention, namely: First, psychological care. The nursing staff actively communicated with the patients, informed

the patients about the disease-related knowledge and the purpose of the surgical treatment to improve the patients' awareness of the disease, and eliminate the patients' inner anxiety and nervousness. After the operation, the patients' family members were actively instructed to encourage the patients, so that the patients could fully feel the love of family and friends, keep cheerful mood, relieve depression and anxiety. Second, posture care. After the operation, the patients were instructed to take a supine position with the head turned to one side, and the patients abdomen was gently massaged with proper massage manipulation and intensity to promote abdominal blood circulation and reduce abdominal pain and distention. Third, pain care. The patients' vital signs were monitored postoperatively, the analgesic tube unit was timely started and the patients' pain was evaluated at intervals of four hours, the amount of analgesic drugs was timely adjusted to help alleviate the pain intensity (Zheng *et al.*, 2018). Soothing music could also be played to keep the patients relaxed, divert the patients' attention, which helped ease the patients' traumatic pain. Fourth, early functional exercise. After the operation, patients were encouraged to take off-bed activity as soon as possible to enhance the body's immunity, promote gastrointestinal motility and avoid abdominal distension. Fifth, closely monitor the patients' vital signs, instruct patients to pay attention to bed rest, reasonable diet, focus on dietary nutrition and relax the mind. The two groups were compared in terms of two-year postoperative recurrence and pregnancy.

Statistics were made for the incidence of adverse reactions, postoperative VAS score, HAMD score, HAMA score, and nursing satisfaction. SPSS21.0 statistical software was used, and the measurement data were expressed by mean \pm SD, and the count data were expressed by (n, %). t and χ^2 were used for comparison between groups. When $p < 0.05$, statistical value exists.

Results

Patients in the study group were aged 23 to 46 years old with an average of 35.8 ± 2.1 years. The reference group patients were aged 24 to 44 years with an average of 34.2 ± 2.6 years. The data of the two groups were comparable ($p > 0.05$).

Table I shows the comparison in two-year postoperative recurrence and pregnancy between the two groups shows no significant difference between the two groups, $p > 0.05$. Table I shows the comparison of postoperative VAS score, HAMD score, HAMA score and nursing satisfaction between the two groups. Comparison of the indicators shows that the study group is superior to the reference group, $p < 0.05$.

Table I. Comparison of recurrence and pregnancy status between the two groups.

Group	Study group	Reference group	t/X ²	p
1-year postoperative recurrence rate (%)	6(6.67)	7(7.78)	0.12	>0.05
2-year postoperative recurrence rate (%)	12(13.33)	11(12.22)	0.2	>0.05
2-year postoperative cumulative pregnancy rate (%)	60(66.67)	58(64.44)	0.39	>0.05
2-year postoperative natural pregnancy rate (%)	42(46.67)	40(44.44)	0.06	>0.05
2-year postoperative IVF-ET pregnancy rate (%)	18(20.00)	18(20.00)	0	>0.05
VAS score	0.99±0.11	3.24±1.35	5.4	<0.05
HAMD score	10.53±2.39	16.59±2.16	7.69	<0.05
HAMA score	9.15±3.26	13.28±5.48	11.25	<0.05
Nursing satisfaction	88(97.78)	65(72.22)	8.64	<0.05

Table II shows the comparison of incidence of adverse reactions between the two groups, in which the reference group has relatively higher irregular uterine bleeding rate than the study group, $p < 0.05$; while other variables of abnormal liver function, abnormal bone density, and add-back did not significantly differ between the groups ($P > 0.05$).

Table II. Comparison of adverse reaction rates between the two groups (n %).

Group	Study group	Reference group	p
Abnormal liver function	5(5.56)	7(7.78)	<0.05
Abnormal bone density	6(6.67)	5(5.56)	<0.05
Add-back	5(5.56)	7(7.78)	<0.05
Irregular uterine bleeding	6(6.67)	20(22.22)	0.001

Discussion

At present, it has been relatively common to treat patients after endometriosis operation with GnRH-a, which can positively improve various symptoms such as dysmenorrhea, pelvic pain and sexual pain, reduce the lesion and lower postoperative recurrence. However, it brings poor medication response of low level of estrogen. Its long-term application will reduce bone mineral density, so the treatment is usually controlled within six months. Due to the high price, it has not been widely used in primary hospitals. Gestrinone is a 19-nortestosterone derivative with potent antiprogesterin activity and moderate antiestrogenic effects. It is also resistant to gonadotropins, which reduces the secretion of gonadotropins from the hypothalamus and pituitary axis, inhibits ovulation and lowers the level of estrogen in the body, inhibits the growth of endometrium and ectopic lesions. Moreover, it has weak androgenic activity, which increases the level of free androgen in

the body, directly inhibits endometrium, thereby leading to ectopic endometrial atrophy and even absorption with significant clinical outcome (Yamabe *et al.*, 2019; Chen *et al.*, 2019). In addition, occasional adverse reactions will occur after medication of gestrinone, including impaired liver function and irregular uterine bleeding, which can be restored after the drug withdrawal without interrupting the medication. In this study, comparison of two-year postoperative recurrence and pregnancy between the two groups showed that treatment with GnRH-a alone had an effect comparable to that of treatment with GnRH-a and gestrinone (Gao *et al.*, 2019).

Meta-analyses of previous studies show the efficacy of GnRH agonists just as in our study. There is a considerable reduction in endometriosis recurrence and pain ratings when hormonal suppression (GnRH agonist) occurred within 6 weeks following endometriosis surgery (Zakhari *et al.*, 2021; Veth *et al.*, 2021). But there is no study on the combination of GnRH-a and gestrinone. So, to our knowledge, this study is for the first time reporting the significantly lower irregular uterine bleeding after the treatment by adding gestrinone to GnRH-a regimen.

Comprehensive nursing intervention is centered on nursing procedure, which is to systematize nursing, improve the quality of clinical nursing, and provide patients with more comprehensive and high-quality comfortable nursing services to promote patient recovery as soon as possible (Zhu *et al.*, 2021). Comprehensive nursing intervention involves pre-operative psychological intervention, elimination of pre-operative anxiety and restlessness to improve treatment confidence and compliance. Postoperative psychological intervention is to stabilize postoperative mood, improve various negative emotions, increase postoperative pain tolerance and promote postoperative rehabilitation (Wang *et al.*, 2021). In posture care program, patients take a comfortable position which prevents operative site traction in abdominal surgery

due to improper lying position, and lowers surgical pain. By abdominal light massage, abdomen blood circulation is boosted to relieve abdominal distension and traumatic pain. Pain care is to start analgesic device as soon as possible after surgery, measure pain intensity at intervals of 4h, adjust analgesic dose, etc., lower pain intensity and speed up postoperative recovery (Zhu et al., 2021; Wang et al., 2021). Comparison of postoperative VAS score, HAMD score, HAMA score and nursing satisfaction between the two groups shows that the study group is superior to the reference group, $p < 0.05$.

Wu et al. (2021) study has shown efficacy of comprehensive nursing on HAMD score and HAMA score but for other disease. But, Zhu et al. (2021) and Wang et al. (2021) studies have shown benefits of comprehensive nursing on endometriosis patients as well as our study.

Conclusions

This is the first trial to show that adding gestrinone to the GnRH-a regimen resulted in much less irregular uterine hemorrhage while having the same long-term efficacy in preventing recurrence of the endometriosis when compared to sole GnRH-a.

Statement of conflict of interest

The authors have declared no conflict of interest.

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