

# Effects of laparoscopic ovarian endometriosis cystectomy combined with postoperative GnRH-a therapy on ovarian reserve, pregnancy, and outcome recurrence

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## Summary

**Objective:** The aim of this study was to investigate the impacts of laparoscopic ovarian endometriosis cystectomy combined with postoperative GnRH-a therapy on ovarian reserve, pregnancy outcome and recurrence. **Materials and Methods:** This was a prospective control study. The experimental group: 63 patients with combinations of laparoscopic bilateral ovarian endometrial cystectomies and gonadotropin-releasing hormone agonist (GnRH-a) treatment for three months. Control group: 62 patients with laparoscopic bilateral ovarian endometrial cystectomies. **Benchmarks:** the changes of follicle stimulating hormone (FSH) and FSH / luteinizing hormone (LH), estradiol (E2) in preoperative and postoperative three months or menstrual two to three days, menstrual two to three days after surgery, natural pregnancy, and cyst recurrence in 18<sup>th</sup> month during postoperative follow-up. **Results:** In experimental group after six months, the percentage of returned FSH accounted for 95.3% of normal range, in the control group it was 82.2%, and the difference was significant ( $p < 0.05$ ). The natural pregnancy rate of preoperative infertility patients (57.1%) was higher than the control (36.8%) ( $p < 0.05$ ). The recurrence rate of preoperative infertility patients (12.7%) was lower than the control (27.4%) ( $p < 0.05$ ). **Conclusion:** After bilateral laparoscopic ovarian endometrial cystectomy, an implement of GnRH-a therapy can improve the postoperative pregnancy rate, which changes with clinical stage and patient age, reduces ovarian recurrence, and its influence on ovarian reserve is lesser.

**Key words:** Laparoscopic ovarian endometrial cystectomy; Ovarian reserve; Sex hormone; Pregnancy outcomes; Recurrence.

## Introduction

With the rapid development of laparoscopic surgery, the incidence of endometriosis (EM) has increased annually, has become a common gynecological disease, and has been referred to as “benign cancer” and “the pelvic sandstorm”. The chronic pelvic pain, dysmenorrhea, and infertility caused by EM impact on women’s health and quality of life seriously. Its pathogenesis, metastasis, invasion, and recurrence are unclear; after years of researches, there are still many unanswered questions, so it has become an intractable disease. Ovarian endometriosis cysts are the most common type in EM (about 17%~44% of pelvic endometriosis) [1]. For EM patients in childbearing age, the principles of laparoscopic conservative surgery surrounding clear diagnosis, reductive lesions, reductive pain, and promotive fertility have been widely accepted and became a preferred option. However, there have been uncertainties regarding laparoscopic ovarian endometrial endometriosis ovarian cystectomy, including its impact on residual endocrine function, the possibilities of residual ovarian syndrome and premature failure, and continuous drug treatment for easy recurrence. Ovarian reserve of women in childbearing age has especially attracted attention in recent years. At present,

there are a large number of studies that have shown that after laparoscopic ovarian EM cystectomy, there was a decline in ovarian reserve and even the risk of ovarian senilism, recurrence, infertility, and other related problems; therefore in recent years it has drawn many attention with the rapid evolution of laparoscopic surgery.

Ovarian reserve, including the number and quality of remaining follicles, reflects female fertility. The decreased functional reserve is caused by the consumption of follicle and decline of their quality. A number of studies have shown that the basic hormones: follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) are important indicators to evaluate ovarian reserve. During the second or third day of menstruation, FSH < 10 mIU/ml, FSH / LH < 3.6, and E2 < 80 pg/ml are regarded as normal [2]. Gonadotropin-releasing hormone agonist (GnRH-a) is an internationally recognized prevention for EM recurrence and is the most effective drugs, and plays an important role in reproduction.

Therefore, this study was designed to observe laparoscopic bilateral ovarian endometrial cystectomy combined with postoperative GnRH treatment for three months, and there set two groups (the combined treatment; the control), the differences of FSH, FSH/luteinizing hormone (LH), and estradiol (E2) changes between the two groups preoperatively and postoperatively three months or during the second or third day of menstruation, menstrual two to three

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Revised manuscript accepted for publication January 24, 2013

days after surgery at six months were compared, and natural pregnancy and recurrence 18 months after surgery were followed to explore the impact of laparoscopic bilateral ovarian EM cystectomy combined with postoperative GnRH-a treatment on ovarian reserve, pregnancy outcome, and recurrence.

## Materials and Methods

### Objects

There were 125 childbearing cases with laparoscopic bilateral ovarian endometrial ectopic cystectomies from April 2008 to May 2010 in the present hospital. This study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics Committee of Changji No 2 People's Hospital. Written informed consent was also obtained from all participants. All patients with married, with normal preoperative menstrual cycles experiencing surgeries at menstrual seven to ten days, had preoperative infertility, and pelvic pain were recorded. According to the revised American Fertility Society (AFS) staging, bilateral ovarian endometriosis lesions were divided into II (36 cases), III (59 cases), and IV(18 cases). According to AFS staging, all cases were divided into two groups, 63 patients in the experimental group combined with GnRH-a treatment for three months; 62 patients in control group without special treatment. The two groups' ethnicities, ages had no statistical differences.

Exclusion criteria: before surgery the patient had taken hormone drugs within three months and patients with malignant or suspicion of malignancy.

Ovarian endometriosis cystectomies were implemented under anesthesia and the intraoperative vital signs were monitored by conventional laparoscopy.

### Postoperative treatment

All patients in the experimental group took 3.6 mg GnRH-a every 28-35 days / times according to patient body weight (body weight < 55 kg: every 35 days / times; weight 55 kg ~ 65 kg: every 30 days / times; weight 65 kg: every 28 days / times) for three months continuously after five to eight days after surgery. If some low-estrogen indications emerged, such as hot flashes, sweating, irritability, and others, a detection of the levels of estrogen were assessed; if necessary add-back therapy was applied, that is, oral tibolone one tablet (2.5 mg) daily at the same time every day continuously, until hot flashes and other symptoms were relieved to maintain the basis of estrogen hormone levels at 30-50 (pg / ml) window dose. The control group did not take any medication.

### Detections

At menstrual two to three days FSH, LH, and E2 values were regarded as indicators of ovarian reserve status [3, 4]. In preoperative menstrual two to three days, postoperative three months or at menstrual two to three days, and postoperative six months menstrual two to three days, FSH, LH, and E2 fluctuating levels were detected, there were follow-ups regarding natural pregnancy and recurrence which lasted 18 months.

Serum was collected by centrifugation of blood samples and stored at -20°. (FSH, FSH / LH, E2 double-antibody radioimmunoassay kits were provided, including SN2682-type of  $\gamma$ -counter (inrablock error < 5%, error between groups < 10%).

### Statistical analysis

Preoperative and postoperative levels of sex hormones were measured by t-test (SPSS17.0).

Table 1. — The preoperative characteristics of two groups.

	Experimental group	Control group
Cases (n)	63	62
< 35years old	46	47
> 35 years old	17	15
BMI (kg/m <sup>2</sup> )	20.10 ± 1.33	20.13 ± 1.07

## Results

### General data

The basic characteristics of the two groups with ovarian endometriosis endometriosis are shown in Table 1. There were no significant differences between age and body mass index (BMI) of these two groups.

### Sex hormone

The sex hormone level changes before surgery, at postoperative three and six months are shown in Table 2. The FSH, LH, and E2 levels of experimental group at postoperative three months were significant lower ( $p < 0.05$ , Table 2) compared with the preoperative ones. In the control group at postoperative three months, FSH and LH levels were significant higher ( $p < 0.05$ , Table 2), and E2 was lower ( $p < 0.05$ , Table 2) than the preoperative level. The basal FSH level of experimental group restored to 95.3% of normal range after postoperative six months, while that of the control recovered to only 82.2%, and the difference was statistically significant ( $p < 0.05$ , Table 2).

### Pregnancy outcome

The pregnancy outcome and recurrence after postoperative 18 months, after drug-discontinuation 32-68 days included 63 patients that experienced menstrual back tides in follow-up experimental group, with an average of 42.8 days, as shown in Table 3. After six months the basal FSH level of experimental group recovered to 95.3% of normal range, while in control group it recovered to 82.2%, and the difference was significant ( $p < 0.05$ , Table 3). The number of pregnancies within postoperative 18 months accounted for 19 patients (47.51% of the preoperative infertilities). The spontaneous pregnancy rate of preoperative infertility patients was 57.1%, and was higher than that in the experimental group, which was 36.8% ( $p < 0.05$ , Table 3). The recurrence rate of the experimental group was 12.7%, compared with the 27.4% of control group and the difference was statistically significant ( $p < 0.05$ , Table 3).

## Discussion

The combination of laparoscopic ovarian endometrial cystectomy and postoperative GnRH-a therapy can inhibit FSH and LH secretion, regulate pituitary function and ul-

Table 2. — The serum FSH, FSH / LH, and E2 level changes in two groups before surgery, and at three and six months postoperatively.

	FSH		FSH/LH		E2	
	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group
Before surgery	6.66 ± 2.67	6.64 ± 1.63	1.48 ± 0.7	1.38 ± 0.8	64.38 ± 19.43	59.43 ± 26.74
Postoperative three months	3.25 ± 1.40*	8.90 ± 1.89*	1.2 ± 0.9*	1.8 ± 1.4*	32.75 ± 18.22*	94.12 ± 35.23*
Postoperative three months/ menstrual back tide	6.65 ± 3.75	7.51 ± 4.29	1.36 ± 0.7	1.6 ± 1.2*	58.75 ± 11.21	79.45 ± 2.26*

Compared to the preoperative levels \*  $p < 0.05$ .

Table 3. — The menstrual back tide, natural pregnancy and recurrence at 18 months postoperatively.

Group	Cases	Before surgery		After surgery		Natural pregnancy after surgery			Interval duration	Recurrence cases after 18 m
		Menstrual duration (d)	Menstrual cycle (d)	Menstrual duration (d)	Menstrual cycle (d)	Infertility before surgery	Pregnancy (cases)	Pregnancy (%)		
Experimental group	63	5.0	30.0	5.1	29.5	21	12	57.1	7.0 ± 1.0	8
Control group	62	4.8	0.3	5.0	28.0	19	7	36.8	9.0 ± 1.2	17

timately suppress the secretion of estrogen and progesterone, decreases estrogen E2 to postmenopausal level, which leads to a severe status of the hormone, that is called “ovariectomized state”, it can reduce the activity of ectopic endometrium and narrow the lesions, in order to enable ovarian healing and functional recovery and reduce the recurrence. It has been confirmed that this surgery may remove part of the normal ovarian cortex and medulla [5, 6], that leads to a mechanical irreversible damage [7, 8].

The maintenance of ovarian function is related to the retention of ovarian tissue. The damage to ovarian vessels is inevitable during surgery, especially the growing follicles will be removed during stripping the cysts from ovarian hilum [9]. Insufficient postoperative residual normal ovarian tissue and the nuclear factor in endometriotic lesions promote an inflammatory reaction, and there may be adverse effects on ovarian function [10, 11]. These factors contribute to ovarian function decline after conservative surgery, causing ovarian reserve to decline. This irreversible mechanical damage, localized secondary ischemia of postoperative lesions, the secretion of inflammatory cytokines in pelvic surgery wounds, and infection can cause tissue fibrosis around the ovary, and further lead to its dysfunction and delay postoperative recovery of ovarian function.

There were 125 EM cases with or without laparoscopic ovarian cystectomy women combined with postoperative GnRH-a treatment and their ovarian reserve were assessed. The FSH, LH, and E2 levels of experimental group at three months postoperatively were significant lower ( $p < 0.05$ ) compared with the preoperative levels. In the control group at three months postoperatively, FSH and LH levels were significant higher ( $p < 0.05$ ), and E2 was lower ( $p < 0.05$ ) than the preoperative level. The basal FSH of experimental group restored to 95.3% of normal range after six months postoperatively, while that of the control recovered to only 82.2%, and the difference was statistically significant ( $p < 0.05$ ). It suggested that a simple laparoscopic

ovarian endometriosis cystectomy has short- and long-term impacts on ovarian function to varying degrees. Postoperative combined treatment inhibited the function of pituitary gland, leading to transient decrease of postoperative FSH, LH, and E2 levels. The majority of patients during follow-up had gradually recovered, with no significant impact on ovarian function, which was consistent with clinical studies to a certain extent.

Laparoscopic ovarian endometrial cystectomy combined with GnRH treatment can cause temporary ovarian dormancy, reduce pelvic and uterine blood supply, reduce secretion of inflammatory cytokines in postoperative wound [12, 15], reduce the infiltration of residual lesions in the ovarian cortex, and reduce the invasion of residual lesions to ovulation hole. This is conducive to postoperative ovary restoration, and is a preferred treatment mode for ovarian cyst combined with infertility [16]. Preoperative infertility cases were 28, including 13 cases with primary infertility and 15 cases with secondary infertility: the average of years of infertility was  $3.20 \pm 0.68$ . The results showed that, compared with the preoperative situation (36.8%), postoperative pregnancy rate (57.1%) of infertile patients in the experimental group was significantly higher ( $p < 0.05$ ), suggesting that combined treatment can improve postoperative pregnancy rate significantly, but the effects were related to clinical stage and patient age. Endometriosis with infertility treated with postoperative Zoladex can improve the pregnancy rate significantly. The majority of pregnancies occur at one postoperative year, especially within six months after GnRH-a drug discontinuance, which is a very important period for guided pregnancy. If after 18 months there were no pregnancies, assisted reproductive technology was recommended as soon as possible [17, 18].

Hyperplasia, infiltration, and diffusion are characteristics of endometriosis, an extensive pelvic adhesion and ambiguity of the lesions, surrounding tissues and organs are visible in severe uterine endometriosis, the pelvic anatomical

structure is destroyed, affecting the pick-up and tubal transport, and could cause infertility. The restoration of the anatomical structure must rely on surgery, in separation process there is some risk of lesion rupture, unresectable invisible lesions in the rear pelvic cavity, and deep infiltration, uncompleted reductive surgery caused by the closed uterine rectal fossa, and is a hormone-dependent disease; residual disease may continue growth under ovarian hormones, so its recurrence rate is very high. Jee *et al.* [19] performed a retrospective cohort study to observe the recurrence of ovarian endometrioid cyst after conservative surgery (four groups: postoperative GnRH-a treatment for three, four, and six months; expectation therapy without medication), found that GnRH-a treatment for six months can better control the rate of recurrence. This study included EM cases with or without laparoscopic ovarian cystectomy women combined with postoperative GnRH-a treatment, their recurrences, and curative effects were assessed by follow-up for 18 months. Compared with preoperative phase, the recurrence rate (12.7%) of the experimental group was significant lower than that of the control group (27.4%) ( $p < 0.05$ ). It demonstrated that combined treatment can reduce the recurrence rate significantly, and is related to clinical stage and patient age. The recurrence rates and recurrence intervals had no significant difference ( $p > 0.05$ ).

Recently some scholars [20, 21] have not supported the protective ovarian effect of GnRH-a, owing to the unclear mechanism of this protective function (a large component of human ovaries include primordial follicles, which are not subject to the effect of gonadotropin). Therefore, further researches are required to explore GnRH-a's protective function on ovary.

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