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The optimal time for laparoscopic excision of ovarian endometrioma: a prospective randomized controlled trial

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Abstract

Objective: The purpose of this study was to explore the optimal time of laparoscopic cystectomy for unilateral ovarian endometrioma patients and to evaluate the influence on the ovarian reserve. Design: Prospective randomized controlled study. Setting: University hospital Population or Sample:88 patients received their first identified diagnosis of ovarian endometrioma by ultrasound (>4 cm) and were given oral contraceptive pills (OCP, drospirenone and ethinylestradiol) for one cycle before laparoscopy. Methods:Randomly divided into two groups: laparoscopy at Late luteal phase (group LLP) (n=44): Termination of OCP for 2 days; and laparoscopy at Early follicular phase (group EFP) (n=44): Day 3 after menstruation. Main Outcome Measure(s): Serum Anti-Müllerian hormone (AMH) and Leukocyte esterase (LE) levels of endometrioma wall were measured. Assessment of ovarian reserve damage based on alterations in the serum AMH levels after unilateral ovarian endometrioma surgery. Result(s): Preoperative serum AMH levels of both group decreased from preoperative to post-operative 1 week and post-operative 6 months, while difference values of group EFP were larger than those of group LLP at post-operative 1 week and post-operative 6 months respectively(1.87±0.97 vs 1.31±0.93, P¡0.01; 1.91+-1.06 vs 1.54+-0.93, P¡0.01);the mean rates of post-operative serum AMH decline were 37.92% and 46.34% in group EFP respectively, which were significantly higher than those of group LLP (25.83% vs 31.43%,P¡0.01). Ovarian endometrioma wall AMH of group LLP was significantly lower than that of group EFP ([22.86+-3.74] vs [31.02+-5.23], P¡0.01);While ovarian endometrioma LE concentration of group LLP was significantly higher than that group EFP([482.83+-115.88] vs [371.68+-84.49], P¡0.01). And significant negative correlation between leukocyte esterase and AMH concentration in the cyst wall of ovarian endometrioma (r=-0.564,P¡0.01). **Conclusion(s):** The optimal time for laparoscopic cystectomy for patients with first identified unilateral ovarian endometrioma is late luteal phase, which reduces ovarian tissue loss and preserves ovarian reserve effectively and safely.

Title:The optimal time for laparoscopic excision of ovarian endometrioma: a prospective randomized controlled trial

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Contribution to Authorship: Qing Wu and Tan Lin not only conceived and designed the study but also participated in the drafting and writing of the manuscript. They also supervised the study and critically revised the manuscript. Qing Wu, Qingmei Yang, and Yanling Lin collected the clinical data. Qing Wu, Qingmei Yang and Tan Lin were responsible for drafting and writing the manuscript and conducting statistical analyses. All the authors substantially contributed to the revision of the manuscript.

Attestation Statement: The subjects in this trial have not concomitantly been involved in other randomized trials. Data regarding any of the subjects in the study has not been previously published unless specified. Data will be made available to the editors of the journal for review or query upon request.

Data Sharing Statement: The data from this study is not publicly available due to ethical and legal restrictions. However, data may be made available upon reasonable request to the corresponding author.

Trial registration: This study registered under the clinical trial registry number (ChiCTR1800019766).

Capsule: The optimal time for laparoscopic cystectomy for patients with first identified unilateral ovarian endometrioma is late luteal phase, which reduces ovarian tissue loss and preserves ovarian reserve effectively.

Acknowledgements: We are grateful to everyone involved in carrying out the study, analyzing the data, and producing the manuscript.

Abstract

Objective: The purpose of this study was to explore the optimal time of laparoscopic cystectomy for unilateral ovarian endometrioma patients and to evaluate the influence on the ovarian reserve.

Design: Prospective randomized controlled study.

Setting: University hospital

Population or Sample:88 patients received their first identified diagnosis of ovarian endometrioma by ultrasound (>4 cm) and were given oral contraceptive pills (OCP, drospirenone and ethinylestradiol) for one cycle before laparoscopy.

Methods:Randomly divided into two groups: laparoscopy at Late luteal phase (group LLP) (n=44): Termination of OCP for 2 days; and laparoscopy at Early follicular phase (group EFP) (n=44): Day 3 after menstruation.

Main Outcome Measure(s): Serum Anti-Müllerian hormone (AMH) and Leukocyte esterase (LE) levels of endometrioma wall were measured. Assessment of ovarian reserve damage based on alterations in the serum AMH levels after unilateral ovarian endometrioma surgery.

Result(s): Preoperative serum AMH levels of both group decreased from preoperative to post-operative 1 week and post-operative 6 months, while difference values of group EFP were larger than those of group LLP at post-operative 1 week and post-operative 6 months respectively(1.87±0.97 vs 1.31±0.93, P¡0.01; 1.91+-1.06 vs 1.54+-0.93, P¡0.01);the mean rates of post-operative serum AMH decline were 37.92% and 46.34% in group EFP respectively, which were significantly higher than those of group LLP (25.83% vs 31.43%,P¡0.01). Ovarian endometrioma wall AMH of group LLP was significantly lower than that of group EFP ([22.86+-3.74] vs [31.02+-5.23], P¡0.01);While ovarian endometrioma LE concentration of group LLP

was significantly higher than that group EFP([482.83+-115.88] vs [371.68+-84.49], P¡0.01). And significant negative correlation between leukocyte esterase and AMH concentration in the cyst wall of ovarian endometrioma (r=-0.564,P¡0.01).

Conclusion(s): The optimal time for laparoscopic cystectomy for patients with first identified unilateral ovarian endometrioma is late luteal phase, which reduces ovarian tissue loss and preserves ovarian reserve effectively and safely.

Key words: laparoscopy, endometriosis, ovarian reserve, AMH, menstrual cycle.

Introduction

Endometriosis (EMT) is a common gynecological condition characterized by the presence of endometrial tissue outside the uterine body resulting in dysmenorrhea, chronic pelvic pain, pelvic masses and infertility, which can seriously affect a woman's health and quality of life. Ovarian endometrioma are the most common type of EMT, with a prevalence of 17%-44% in patients with endometriosis(1).

Laparoscopic cystectomy has become the gold standard in the surgical management of persistent adnexal masses including ovarian endometriosis,with the surgical aim of removing all visible endometriosis lesions and restoring anatomy(2). But ovarian cystectomy may harm ovarian reserves(3-5). Surgical procedures on the ovaries lead to ovarian tissue damage, which can strip normal ovarian tissue and exacerbate the harm to the remaining follicles, which raises concerns of gynecologists regarding the use of different surgical procedures in this field(6, 7). However, few studies have focused on the optimal time of surgery on ovarian endometrioma.

Anti-Mullerian hormone (AMH) is produced by the granulosa cells of primary, preantral, and small antral follicles, but not primordial follicles. AMH level indirectly represents the quantity of the ovarian follicle pool, estimated by the number of early growing-stage follicles. Moreover, the serum AMH level appears to be independent of the menstrual cycle and is not affected by the use of gonadotropin-releasing hormone (GnRH) agonists or oral contraceptives(8-11). Therefore, serum AMH levels, as a promising and reliable parameter, has been used to assess the ovarian reserve around treatments which potentially cause ovarian damage(12-15).

To date, there has been no clear data on whether laparoscopic endometrial cystectomy, with different menstruation phase, will reduce the damage of ovarian function, shorten the operation time, reduce intraoperative blood loss and accelerate patient recovery. Therefore, the purpose of this study was to explore the optimal timing of the first laparoscopic cystectomy in ovarian endometrioma patients with unilateral and to evaluate the influence on the patient's ovarian reserve.

Material and methods

This prospective clinical study was approved by the board of Fujian provincial hospital ethics committee(2018ky0024), and registered under the clinical trial registry number (ChiCTR1800019766). Preoperative informed consent was taken from all patients after providing explanations of the possible risks and complications. 88 patients with unilateral ovarian endometriomas were recruited into this prospective study in the Department of Obstetrics and Gynecology in Fujian provincial hospital from March 2019 to March 2021. After inclusion in the study, all patients were given oral contraceptive pills (drospirenone and ethinylestradiol) for 1 cycle to determine the timing of surgery. Inclusion criteria were as follows: 1) age 20–36 years; 2) regular menses, 3) clinical and ultrasonographic finding of unilateral ovarian endometrioma [?] 4 cm first time. 4) without pregnant and plan of getting pregnant in the following 6 months. Exclusion criteria were the following: 1) any suspicious finding of malignant ovarian diseases; 2) ovarian, uterine, tubal surgery history; 3) endocrine disease and treatment history; 4) long-term use of hormonal drugs for more than 3 months (e.g., gonadotropin-releasing hormone analogs); 5) chronic diseases; 6) smoking. Prior to enrollment, the study objectives and steps were explained to all patients. Patients who fulfilled the inclusion criteria and consented to participate in the study were enrolled.

Randomization

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Randomization was performed at a 1:1 ratio according to a computer-generated number list into two groups. The randomized number was concealed in an opaque, sealed envelope for each enrolled patient, and the envelopes were opened consecutively by a study nurse in the clinic before the surgery after verbal and written consent. The single number drawn was included in the late luteal phase group (LLP) and the double number was included in the early follicular phase group (EFP) .

Surgical Technique

All surgeries were performed by the same surgeon with extensive experience in endometriosis surgery, particularly aware of the necessity to avoid damaging or removing healthy ovarian tissue. Laparoscopic pneumoperitoneum was induced by CO2 insufflation with a Verres needle. Umbilical 10-mm trocar and telescope entries were performed. Another three trocars were inserted through lower abdominal incisions, under direct laparoscopic vision. After mobilization of the cystic adnexa, ovarian cystectomy was performed by incising the ovarian cyst with cold scissors and carefully identifying, separating and completely removing the entire cystic wall from the ovarian cortex by traction/counter traction using non-traumatic grasping forceps. Hemostasis was achieved with careful, highly selective, 3-0 absorbable sutures (Vicryl; Ethicon Inc., New Jersey, USA) without any electrocoagulation devices.

The blood loss was estimated by combining the volume of blood collected within the suction canister and the weight of gauze used during surgery. The stage of the endometriosis was determined referring to the revised classification of the American Society of Reproductive Medicine (r-ASRM)(16).

Tissue sample collection

After naked eye examination of the entire cyst wall, five pieces of the specimen of 5mm2 obtained from cyst walls at different portions, one was from the intermediate part of the specimen,the others were from the four quadrants respectively. Other cyst walls were sent to the pathology laboratory, and diagnosis of ovarian endometriosis was confirmed by pathologic examination. The leukocyte esterase concentration and tissue AMH levels in the cyst wall were measured using (LE/AMH) ELISA kit (Jiangsu Meimain Co., Ltd., Jiangsu, China). All hormonal measurements were also performed in the same reference laboratory.

Hormonal assays

All patients had taken serum specimens before general anesthesia, 1 week and 6 months postoperatively. Venous blood samples were obtained and serum were extracted by centrifugation. Serum E2 and P level was measured by enzyme-linked fluorescent assay (ELISA; Beckman Coulter Inc., Ireland) according to the manufacturer's instructions. Serum AMH level was measured by a commercially available enzyme linked immunosorbent assay kit (ELISA; Beckman Coulter Inc., Ireland) and reported as nanograms per milliliter with the detection limit of 0.16 ng/ml.

Unilateral ovarian involvement

We compared the potential role of unilateral ovarian involvement on preoperative levels and postoperative changes in AMH values after laparoscopic endometrioma excision. AMH decline (% decline AMH) was used to compare the changes in AMH levels in endometrioma resected at different menstrual cycles. The rate of AMH decline was calculated using the following formula: (% decline AMH) = (preoperative AMH level – AMH at 1week or 6 months post-operatively)/ preoperative AMH level.

Statistical analysis

Categorical variables were described using proportions. Baseline patient characteristics were calculated via t-test for comparisons of normally distributed data and the rank-sum test for comparisons of non-normally distributed data. Count data were summarized as percentages and compared using the chi-square test and Fisher's exact tests. The analysis of variance (ANOVA) was used in intra-group comparison at different time-points. The two-sided P value less than 0.05 was considered to be significant. The relationship between Ovarian endometrioma wall AMH and leukocyte esterase concentration were generated based on significant pearson correlations between data. Correlations with p value < 0.05 were considered significant. All data

were analyzed with the SPSS version 26 (IBM Corp., Armonk, NY, USA) and PRISM version 9.0 (GraphPad Software, La Jolla, CA, USA).

Results

Baseline Characteristics

There were no significant differences in age, cyst size, Gravidity, Parity, dysmenorrhea, r-AFS Staging, Blood loss volume and Operation time between the two groups in this study. Serum progesterone was significantly higher in Late luteal phase than in early follicular phase on the day of surgery ([2.46 +- 1.43] vs [0.43 +- 0.34]; P < 0.01) Table1.

AMH as the biomarker to evaluate ovarian reserve and follicle loss

There is no significant difference about preoperative AMH between the two groups. The serum AMH values at 1 week after surgery were higher in group LLP than that in group EFP ([3.58+-1.65] vs [3.02+-1.22], P=0.08). However, the AMH decrease value was significantly lower than that of group EFP ([1.31+-0.93] vs [1.87+-0.97], P<0.01). Serum AMH at post-operative 6 months in group LLP were significantly higher than that in group EFP ([3.35+-1.67] vs [2.61+-1.15], P = 0.02), while AMH decrease values at post-operative 6 months were significantly higher in group EFP than that in group LLP ([1.54+-0.93] vs [1.91+-1.06]; respectively: P< 0.01) Table 2.

The mean rates of post-operative serum AMH decline were 37.92% and 46.34% in group EFP respectively, which were significantly higher than those of group LLP (25.83% vs 31.43%)(P¡0.01) see Table 3.

Ovarian endometrioma wall AMH of group LLP was significantly lower than that of group EFP ([22.86+-3.74] vs [31.02+-5.23], P¡0.01); While ovarian endometrioma leucocyte esterase concentration of group LLP was significantly higher than that group EFP ([482.83+-115.88] vs [371.68+-84.49], P¡0.01) see table 4 and Figure 1. And significant negative correlation between LE and AMH concentration in the cyst wall of ovarian endometrioma (P¡0.05) see Figure 2.

Discussion

Laparoscopic endometrioma cystectomy is a recommended and widely used method because it meets the diagnosis and treatment goals of endometriosis, which can reduce pain, increase the chance of spontaneous pregnancy, and reduce disease progression and recurrence(17-19). However, in addition to the possible negative effect of endometriosis itself on ovarian reserve, serum AMH levels were also significantly decreased after laparoscopic cystectomy for endometrioma(5, 20-24). Since the ovarian reserve responds to the reproductive function of the woman, it must be preserved ultimately during laparoscopic cystectomy.

Anti-Mullerian Hormone (AMH) is a member of the transforming growth factor-β family and secreted by primary, preantral, antral follicles(25). AMH levels correlate with the number of growing follicles, and do not change significantly during menstrual cycle(14, 26). Therefore, AMH has been used to predict the decline of ovarian function, and is the preferred biomarker of ovarian reserve(27, 28).

Several hypotheses have been formulated to explain the relationship between cyst excision and reduction of the ovarian reserve. Some authors demonstrated that the removal of ovarian endometrioma, which is commonly characterized by absence of a clear plane of cleavage between the endometrioma cyst and ovarian tissue, could result in unintentional removal of the ovarian cortex and loss of follicles, with potential reduction in follicular reserve(29, 30). The amount of ovarian parenchyma loss seems to increase proportionally to the increase in cyst diameter(31). According to this hypothesis, damage to the ovarian reserve can be a consequence to permanent loss of ovarian tissue, and should then persist over time after surgery(21).

This study was dedicated to investigate surgical optimal timing to perform cystectomy which can reduce damage to ovarian function by evaluate for the first time the serial changes in serum AMH levels after laparoscopic endometriosis cystectomy for endometriosis and evaluate ovarian endometrioma wall AMH and ovarian endometrioma leucocyte esterase concentration.

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Our results showed that serum AMH levels decreased significantly at 1 week and 6 months after surgery, but the decreasing trend of serum AMH levels in group LLP was significantly lower than that in group EFP. A systematic review and meta-analysis study showed that the median preoperative AMH level was 3.1 ng/mL, which significantly decreased to 1.51 ng/mL within 1-9 months after surgery, with a decline rate of 51.29%(3). In a prospective longitudinal study showed that the rate of decrease in AMH was 52.2%, 53.7%, 54.8% at 1, 3, 6 months after surgery compared to that of baseline levels, respectively(32). In this study, compared to baseline levels, patients who underwent surgical treatment at late luteal phase had AMH decline rates of 25.8% and 31.4% at 1 week and 6 months postoperatively, respectively. However, patients treated surgically at the early follicular phase had AMH decline rates of 37.9% and 46.3% at 1 week and 6 months postoperatively, respectively. Hoang Tong et al. found that unilateral ovarian cystectomy with a 43.4%-48% decrease in serum AMH from 1-6 months after surgery was basically the same with the results of cystectomy performed in the early follicular phase in this study. Zhou Liu et al. reported that the distance to restore ovarian reserve after laparoscopic unilateral ovarian cystectomy was estimated to be 6 months. Urman et al., found a significant decrease both in AMH concentration and in antral follicle count (AFC) one month after surgery, a reduction that persisted at six months postoperatively(33). So we suppose that laparoscopic cystectomy for unilateral ovarian endometrioma at late luteal phase may reach a content result about follicle loss and ovarian reserve.

The study also found that ovarian endometrioma wall AMH of group LLP in patients with first cystectomy was significantly lower than that of group EFP ([22.86±3.74] vs [31.02±5.23], P¡0.001); While ovarian endometrioma leucocyte esterase concentration of group LLP was significantly higher than that group EFP ([482.83+-115.88] vs [371.68+-84.49], P¡0.001). Significant negative correlation between leukocyte esterase and AMH concentration in the cyst wall of ovarian endometrioma (P¡0.05). From our results, it appears that ovariectomy with different menstrual cycles is likewise an important factor in the rate of decrease in AMH levels after laparoscopic ovarian cystectomy in patients with endometriosis. We supposed that the density of the border between endometrioma and normal ovarian tissue may fluctuate during the menstrual cycle, and that the loosening of the border and inflammatory edema of the tissue allow the cyst wall to be more easily peeled off in the late luteal phase, reducing the loss of normal ovarian tissue.

There are some limitations in this study. First, this study analyzed data of one single center. Second, this study was conducted only in patients with first identified single ovarian endometrioma and the result should not available for patients who had previous endometrioma and previous pelvic surgery. Third, patients with bilateral ovarian endometrioma cysts were not collected and this study only had a short follow-up period (6 months).

In conclusion, our study suggests that laparoscopic cystectomy in the late luteal phase is an advantageous option for patients with endometrioma found for the first time to reduce ovarian tissue loss and preserve ovarian reserve effectively and safely. However, more prospective studies, longer follow-up and data from multiple centers are need to support clinical practice and underlying mechanisms are needed.

Declarations

Funding

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Ethical approval and consent to participate

Ethical approval (2018ky0024) to conduct the study was provided by the Institutional Ethics Committee of Fujian provincial hospital ethics committee, and registered under the clinical trial registry number (ChiCTR1800019766).

Consent for publication

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Not applicable.

Competing interests

The authors declare that no competing interests exist.

Availability of data and material

The data from this study is not publicly available due to ethical and legal restrictions. However, data may be made available upon reasonable request to the corresponding author.

Contribution to authorship

Qing Wu and Tan Lin not only conceived and designed the study but also participated in the drafting and writing of the manuscript. They also supervised the study and critically revised the manuscript. Qing Wu, Qingmei Yang, and Yanling Lin collected the clinical data. Qing Wu, Qingmei Yang and Tan Lin were responsible for drafting and writing the manuscript and conducting statistical analyses. All the authors substantially contributed to the revision of the manuscript.

Acknowledgements

We are grateful to everyone involved in carrying out the study, analyzing the data, and producing the manuscript.

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