Relapse after conservative surgery combined with Triptorelin Acetate versus conservative surgery only in women with focal adenomyosis: study protocol for a multicenter, prospective, randomized controlled trial

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Study protocol

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Abstract

Background: To preserve fertility or integrity of organs was on the rise for the most women with adenomyosis. Adenomyomectomy is now a widely applied conservative surgery, however relapse is a serious problem after operation. Postoperative treatment, such as gonadotropin-releasing hormone agonist (GnRHa) has been suggested to result in reducing the recurrence rate in patients. However, there is still a lack of evidence from randomized clinical trials comparing the efficacy of GnRHa for decreasing the postoperative recurrence rate. Method/Design Relapse after conservative surgery combined with Triptorelin Acetate versus conservative surgery only in women with focal adenomyosis is a multicenter, prospective, randomized controlled trial. The primary outcome is relapse accessed with Visual Analogue Scale (VRS) and Numeric Rating Scale (NRS), Pictorial blood loss assessment chart (PBAC) score and the size of uterus and lesion are measured by two/three-dimensional color doppler ultrasonography (2D/3D-CDUS) or magnetic resonance imaging (MRI). The secondary outcomes include quality of life, clinical pregnancy, ovarian reserve, and adverse events, assessing by Short Form (36) Health Survey and Female Sexual Function index, serum follicle-stimulating hormone, estradiol levels and anti-muellerian hormone and so on. All these indexes are measured at 3, 6, 12, 18, 24, 30, 36 months after conservative surgery. Discussion The result of this large multicenter randomized trial will provide evidence for one of the strategies of long-term management in focal adenomyosis after conservative operation.

Background

Adenomyosis is a common gynecologic benign disorder characterized by aberrant presence of endometrial glands and stromal within the myometrium[1-3]. The main symptoms are dysmenorrhea, chronic pelvic pain, dyspareunia, abnormal uterine bleeding (especial for heavy menstrual bleeding) and infertility, which seriously affect quality of life and work productivity in reproductive women[4, 5].

Hysterectomy considered to be a radical therapy for patients, who were refractory or will not desire to preserve fertility[6, 7]. However, many patients in reproductive age are very sensitive to preserve their fertility and organs[8]. Medical treatments or conservative surgery were options. The former contains non-steroidal anti-inflammatory drugs or hormone regulating drugs, which can keep a hypoestrogenic state, like gonadotropin releasing hormone agonist (GnRHa), danazol, progestogens or oral contraceptive pills[9, 10]. Gonadotropin releasing hormone agonist was the best acceptable treatment for patients in the past 20 years[11]. Unfortunately, these medicines could just provisionally improve symptoms and often lead to serious side effects[12]. Therefore, conservative surgeries come to be another choice, according to the extent of the focus, surgical options were classified into adenomyomectomy (for localized adenomyosis) and partial adenomyomectomy (for diffuse adenomyosis)[4, 13]. The rate of pain relief was higher in focal adenomyosis patients than diffuse adenomyosis women after conservative operation[14]. However, different ratio of systematic relapse was the main issue for this treatment, due to the no clear cut line between focus and normal myometrial tissue[14]. How to control recurrence after surgery has become the current priority.

Recently, some researchers confirmed that surgical-medical treatment provides a more effective treatment option for the symptomatic relief in focal adenomyosis than surgical treatment alone in some prospective or retrospective studies[7, 15, 16]. However, there is still a lack of evidence from randomized controlled study as to confirm whether GnRH agonists could decline the recurrence rate after conservative surgery in women with focal adenomyosis. This study is a multicenter randomized parallel controlled trial comparing efficacy of triptorelin acetate in protecting for relapse of post-operative treatment in focal adenomyosis patients.

Method/design

308 postoperative participants after complete excision of focal adenomyosis are randomly assigned 1:1 to treatment group (triptorelin acetate) and control group. Patients will be recruited at 10 hospitals across Midwest China. All research units have been approved by the ethics committees. Every patient will sign an informed consent prior to this study. This report follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline (Additional file 1).

Inclusion criteria

The inclusion criteria are as follows:

1. Women aged ≥18 and ≤45 years;
2. Women with pathological diagnosis focal adenomyosis;
3. Women who accept complete excision of adenomyosis, did not take any steroid hormone therapy three months before surgery;
4. Women who are health before and not pregnant;
5. Women who can comply with the study procedures and give written informed consent.

Exclusion criteria

1. Women who are also participating in other clinical trials at the same time;
2. Women who are concomitant with have been diagnosed with ovarian endometrioma, deep infiltrating endometriosis, multiple leiomyomas;
3. Women with congenital uterine abnormalities such as uterine malformation (unicornis uterus, septate uterus, or duplex uterus) or acute genital inflammation or malignant tumor;
4. Women who are pregnant;
5. Women who were taken steroid hormone therapy three months before surgery;
6. Women with hereditary disease, blood disease, liver and kidney dysfunction or malnutrition diseases that cause anemia;
7. Women who cannot suffer from surgery or are allergic to triptorelin acetate;
8. Women who are unable to comply with the study procedures and give written informed consent.

Screening and enrolment

Previous medical history and current medication status are reviewed with the standardized case report forms. A physical examination and imaging such as two/three-dimensional color doppler ultrasonography (2D/3D-CDUS) or magnetic resonance imaging (MRI) are performed. Laboratory measurements as serum follicle-stimulating hormone (FSH), Estradiol (E2), anti-muellerian hormone (AMH), cancer antigen 125 (CA125)safety assays include blood routine, urine routine, liver function, renal function, hepatitis virus, HIV, syphilis, coagulation, electrocardiogram (ECG), x-rays are measured in the local department of study sites. Either laparoscopy or transabdominal surgery is performed to completely remove all clinically recognizable lesions in patients who are suspected as focal adenomyosis.

Written informed consent will be obtained from the patients after operation. Quality of life, degree of pain and menstrual volume will be recorded using the Short Form (36) Health Survey (SF-36), Female Sexual Function Index (FSFI), pictorial blood loss assessment chart (PBAC) score, Visual Analogue Scale (VAS) and Numeric Rating Scale (NRS) after confirming by histology. A schedule of enrollment, interventions, and assessment is provided as in the table below (Table 1).

Adenomyomectomy

Laparotomy, hysteroscopy or laparoscopy were all contained in this study. During the laparoscopy, patients are taken the lithotomy position under general anesthesia with endotracheal intubation. After sterilization, pneumoperitoneum was created with carbon dioxide gas at 13 mm Hg (Karl Storz GmbH & Co. KG, Tuttlingen, Germany). Surgery was performed with 4 trocars for surgical instruments. Supine position and median incision are suitable for laparotomy. Hysteroscopic surgery is conducted for type 0 or type 1 adenomyoma (Karl Storz GmbH & Co. KG, Tuttlingen, Germany). Surgical approach is adenomyomectomy. The principle of these surgical options included completely removal of clinical visible lesions, maintained the integrity of uterine wall and keep the integrity of the uterine cavity as much as possible. The length of the surgery, size of the focus, blood loss and the integrity of the uterine cavity should be kept in record.

Interventions

Simple randomization is used to assign qualified participants to surgery only group (Group A) and surgery plus GnRH agonist group (Group B) with a 1:1 ratio. GnRH agonist was used for intervention group, using 3.75mg intramuscular injection (Diphereline, Ipsen, France) at the first day of the menstruation after surgery, then once every four weeks for six courses. The sign and symptoms of hypoestrogenism, including hot flushes, night sweat, sleep disorder, abnormal emotion and osteoporosis, could be caused by GnRH agonist, which should be carefully evaluated and could be treated with Tibolone 1.25 mg per day as add-back therapy to maintain estradiol at 30-50 pg/ml[17].

When intolerable adverse reaction is occurred on Group B patients, intervention will be discontinued or modified. Color doppler ultrasonography and steroid hormone test on the third and 6th month after conservative operation can help to monitor adherence. During the trial, other medication, such as use of steroid hormone or herbal medicine, or intervention, such as levonorgestrel-relesing intrauterine syste (LNG-IUS) will be prohibited. If other medication/intervention is necessary for therapeutic purpose or other reason, which violate our study procedure and consent. The patient will be excluded from final analyses.

Randomization

Eligible participants were assigned subjects to two groups with a 1:1 ratio simple randomization. The sequence of randomization has been set up by biostatisticians in data coordinator center with Microsoft Excel, using function of RAND (). The original sequence is safely kept by the staff in the data coordinator center, and it has been input into the online central randomization system by these staff members, who are not involved in enrolling subjects. The sequence is not accessible to any investigators or study coordinators. If a subject fulfills the enrollment criteria, the authorized study coordinator will get the assignment for her. After randomization, both subjects and investigators are informed about the assignments.

Outcome and outcome assessments

The primary outcome is relapse, which defines as recurrence of dysmenorrhea or pelvic pain or menorrhagia or 2D/3D-CDUS / MRI confirmed local recurrence compared to the baseline image after the surgery at first follow up time. Regarding imaging relapse, maximal diameter of suspicious recrudescent focus increase > 1cm during the follow-up period, measuring by 2D/3D-CDUS or MRI. During the follow up, if a positive finding is found by the same imaging examination should be conducted as a further evidence. In addition, the VRS and NRS are applied for evaluation of dysmenorrhea or pelvic pain and the recurrence was defined as any VRS measure was ≥ 2, NRS measure was ≥ 4. PBAC score is used to predict coagulation disorders in women with menorrhagia and recurrence was defined as score > 100. The proportion of the recurrence at 3, 6, 9,12, 18, 24, 30, 36 months will be followed-up.

The secondary outcomes include quality of life, clinical pregnancy, ovarian reserve, and adverse events. The quality of life is assessed by SF-36 and FSFI, regarding as a measure of health status and sexual functioning in women. Ovarian reserve is evaluated by FSH, E_2 and AMH, the first two are measured before surgery and during the follow-up period at the beginning of the menstrual cycle unless during the treatment of triptorelin acetate. AMH can be measured at any time before and after operation at the time of follow-up. Difference in score for eight dimensions (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role emotional and mental health) of SF-36 and FSFI and mean value of FSH, E_2 and AMH for participants in each group at 3, 6, 9,12, 18, 24, 30, 36 months will be assessed for quality of life and ovarian reserve. The pregnancy intention, pregnancy rate and outcome are recorded in a standard case report form, including abortion, premature delivery, full-term production, to evaluate difference of pregnancy outcome in each treatment arm at 36 months.

The follow-up procedure is acquired from the outpatient department records. Follow-up visits occur at 3, 6, 12, 18, 24, 30, 36 months after conservative surgery.

Treatment-related adverse effects are monitored at each visit. Adverse events are any unfavorable medical occurrences associated with the subject's participation in the research, whether considered related to the study intervention. Serious adverse events are events that are temporally associated with the subject's participation in research that meet any of the following criteria: death, life-threatening, severely or permanently disabling, requiring in-patient hospitalization or prolongation of existing hospitalization, or any events deemed as serious by the local principal investigator. Difference in the proportion of patients for adverse events in each group would be assessed at 36 months.

Data analysis

Sample size calculation

Based on a prospective study revealed a relapse rate for only surgery group was about 49%, and for surgery and GnRH agonist treatment group was 28.1%[7]. A two-tailed test with alpha set at 0.05 and 85% power is used to detect a minimum clinical meaningful difference between control and intervention groups. The minimal sample size is calculated as 139 for each group. In consideration of a dropout rate of 10%, we will totally recruit 308 subjects.

Data collection

Data are collected with a standard case report form. Data are de-identified before being input into the database. Regular study site monitor and database checking are performed to ensure the accuracy of data collected. The data management, monitoring and reporting of this study will comply with the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines.

Data analysis plan

Data analysis and reporting will be conducted in accordance to the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement, which were recorded in our flow chart (Fig. 1), including the number of eligible participants and lost to follow-up for various reasons. Data analysts will be blinded after assignment to interventions. Unblinding of a participant's allocated intervention during the trial is permissible after blind verification and a submission of data locking proof by statistical analyst.

Intention to treat, which is based on the initial treatment intent, will be used as a foundation in our analysis. Participants begin the treatment is part of the trial, whether they finish it or not. The characteristics at baseline will be described between control and intervention groups. Continuous data will be summarized by means and standard deviation with Wilcoxon rank sum test to identify differences of baseline characteristic between two groups. Categorical data will be described by number and percentages, using Pearson chi-square test to compare discrepancy between groups.

The primary outcome measure is the recurrence rate between Group A and Group B after three years' follow-up, which will be analyzed by Pearson chi-square test. For efficacy parameters, such as score of pelvic pain and dysmenorrhea, menstruation blood loss, size of uterus and lesion will be analyzed using generalized estimating equations (GEE) or mixed effects model repeated measures (MMRM) to account for correlations among these observations in different follow up points.

The parameters from secondary outcomes contains SF-36, FSFI, pregnancy rate and pregnancy outcome are calculated during 36 months' follow-up are using generalized estimating equations (GEE) or mixed effects model repeated measures (MMRM) analysis to compare differences between Group A and Group B at different time points.

The number of participants with adverse events (AE) or serious adverse events (SAE) will be presented for each arm. We will not take any formal statistical testing.

Dissemination

The results of the study will be publicated in a peer-reviewed medical journal without use of professional writer. After agreement of the Steering Committee, source data will be shared available through national or international anonymised datasets.

Discussion

To preserve fertility or integrity of organs was on the rise for the number of women with adenomyosis. Compare with relapse after withdrawal of the medical treatment, adenomyomectomy was widely applied. The remission rate of dysmenorrhea or dyspareunia was 50%-94.7% after complete excision and improvement of menorrhagia was 25%-80%[18]. Nevertheless, a symptomatic or local recurrence of the condition remained exist. About 2.8%-13.95% patients were relapsed at the end of first year. 14.28%-49% participants would recurrent in 24 months[18]. Therefore, the long-term management after surgery was the main issue.

Recently, Al Jama retrospectively analyzed 18 patients, accepting adenomyomectomy and GnRHa for 24 weeks, 15 of which had systematic improvement after one year's follow-up [16]. Liu carried out an uncontrolled descriptive study of 186 women with pathologically proven adenomyoma, who underwent ultramini-laparoscopic adenomyomectomy and a 6-month course of goserelin acetate treatment. After 3 years' follow-up, the rate of systematic recurrence was 9% [19]. Wang et al.' prospective non-randomized study found a significant decline of relapse rate in surgical-medical treatment group at the end of 2-year follow-up [7]. However, our retrospective result showed no difference between control and intervention group at the end of first or second year. It is noteworthy that there was a significant difference between control and GnRH agonist group with symptomatic or imaging relapse at the end of 36 months' follow-up. In other words, postoperative treatment might be applied to reduce long-term recurrence rate. If we should use the postoperative method to prevent from relapse in adenomyosis patients is still unknown.

This is the first multicenter, prospective, randomized controlled trial, comparing the efficacy of GnRH agonist in reducing recurrence for focal adenomyosis patients who have had been suffered from adenomyomectomy. We cannot use blinding to trial participants and care providers due to the drug-induced amenorrhea and/ or series of side effect after GnRHa therapy, which will be easy for patients and doctors to speculate the treatments. The lack of blinding might cause substantial bias, especially for the subjective judgment of patients, like pain scoring in primary outcome. To solve this problem, we set up two types of pain scoring system to reduce the chance of subjective error judgment for patients. In addition, if there is no obvious systematic improvement after operation at the first follow up so that participant will change the original treatment. They should withdraw the consent and will be excluded in final analysis.

We plan to enroll 308 subjects from 10 teaching hospitals in China. The enrollment began in March 2018. At the time of manuscript preparation, more than 90 subjects have been enrolled. The result of this large multicenter randomized trial will provide level I evidence for the strategy of long-term management for focal adenomyosis after conservative operation.

Trial status

The Protocol Version is Version 1.0; March 8, 2018. Recruitment began on March 8, 2018. The expected date for recruitment completion is November–October 2019.

Abbreviations

GnRH: Gonadotropin-releasing hormone; VRS: Visual Analogue Scale; NRS: Numeric Rating Scale; PBAC: Pictorial blood loss assessment chart; 2D/3D-CDUS: two/three-dimensional color doppler ultrasonography; MRI: magnetic resonance imaging; SF-36: Short Form (36) Health Survey; FSFI: Female Sexual Function index; FSH: follicle-stimulating hormone; E2: estradiol levels; AMH: anti-muellerian hormone; GEE: generalized e5stimating equations; MMRM: mixed effects model repeated measures

Declarations

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Availability of data and materials

No additional data available

Authors' contributions

WW, XM contributed to the study design and manuscript drafting and revising; SW designed the study, is on the Steering Committee and revised the manuscript; WZ, ZL, YW, ZY, CZ, LH, RL, HX, WW, QY, JW, MZ were involved in the study concept and design and revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Central ethical approval has been confirmed from the Tongji Hospital of Tongji Medical College of Huazhong University Medical Ethics Committee (ref approval no. TJ-IRB20180310) and we will not begin recruiting at other centres in the trial until local ethical approval has been obtained". Written informed consent is obtained from the patients after screening.

Consent for publication

Not applicable

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Table 1

Table 1. schedule of screening, enrollment and assessment.

Evaluation	Screening	Enrolment	Time of follow-up after surgery (month)						
			3	6	12	18	24	30	36
Written consent		√							
Inclusion/exclusion criteria		√							
Medical history	√								
Physical exam	√								
Safety test (preoperative examination)	√								
2D/3D-CDUS /MRI	√		√	√	√	√	√	√	√
FSH, E2, AMH, CA125	√		√	√	√	√	√	√	√
Side effects			√	√	√	√	√	√	√
VAS and NRS		√	√	√	√	√	√	√	√
SF-36 and FSFI		√	√	√	√	√	√	√	√
PBAC score		√	√	√	√	√	√	√	√

Figures

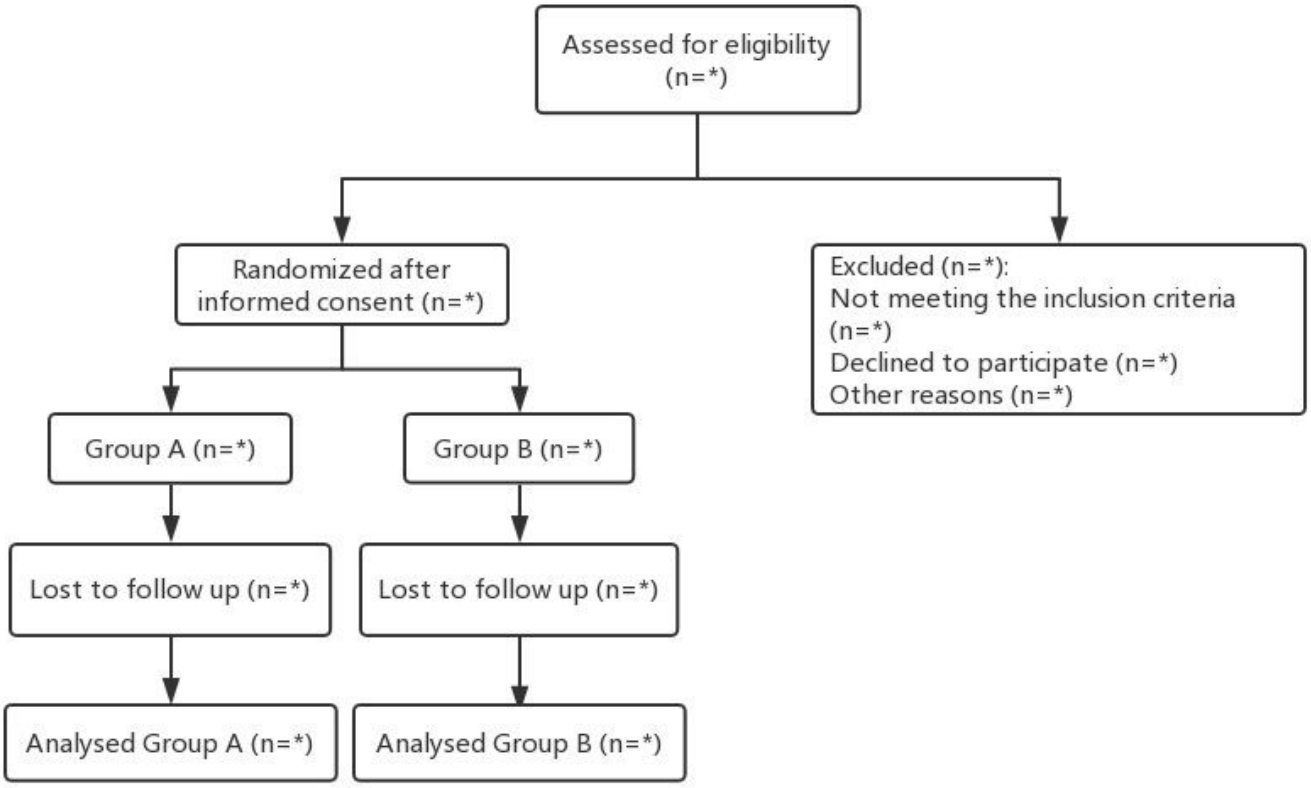

Figure 1

Flowchart of this study.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITChecklistforrandomisedstudies.doc
- newCONSORT2010checklist.pdf