GnRHa vs. observation in the treatment of multiple leiomyomas after myomectomy: study protocol for a multicenter, prospective, randomized controlled clinical trial

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Study protocol

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Abstract

Background: Recurrence of the leiomyoma is one of the major concerns of myomectomy in the long-term management, especially for the multiple leiomyomas. Gonadotropin-releasing hormone agonist (GnRHa) is currently one of the most effective medications to reduce the volume of the fibroids and the uterus. However, its role in preventing recurrence after conservative surgery remains unclear. At present, there is no evidence from randomized clinical trials comparing the efficacy between GnRHa and follow-up observation in the recurrence rate of multiple leiomyomas after myomectomy.

Methods: We are conducting a randomized controlled trial in women aged 18-45 undergoing myomectomy for the multiple leiomyomas. After the surgery, women whose pathological result confirms multiple leiomyoma are randomized into two parallel groups: observation group and GnRHa group. The primary outcome is the recurrence of either clinical symptoms or imaging.

Discussion: The results of this study will provide evidence for the efficacy of the gonadotropin-releasing hormone agonist in preventing the recurrence of high-risk leiomyoma after myomectomy.

Trial registration: Chinese Clinical Trial Registry, ChiCTR-IPR-17012992 (http://www.chictr.org.cn/showproj.aspx?proj=21797). Registered on 15 Oct 2017.

Contributions To The Literature

- Recurrence of the leiomyoma is one of the major concerns of myomectomy in the long-term management, especially for the multiple leiomyomas.
- Gonadotropin-releasing hormone agonist (GnRHa) is currently one of the most effective medications to reduce the volume of the fibroids and the uterus. However, its role in preventing recurrence after conservative surgery remains unclear.
- At present, there is no evidence from randomized clinical trials comparing the efficacy between GnRHa and follow-up observation in the recurrence rate of multiple leiomyomas after myomectomy.
- The results of this study will provide evidence for the efficacy of the gonadotropin-releasing hormone agonist in preventing the recurrence of high-risk leiomyoma after myomectomy.

Background

Leiomyoma, which is also called myoma or uterine fibroid, is the most common benign uterine tumor among women of reproductive age and its clinical presentations include pelvic mass, chronic pelvic pain, abnormal uterine bleeding and infertility (Donnez & Jadoul, 2002). Leiomyoma occurs in 50–60% of women of reproductive age, rising to 70% by the age of 50 (Baird, Dunson, Hill, Cousins, & Schectman, 2003), which translates into 880 million women worldwide. It originates from the smooth muscle cells in the myometrium and highly dependent on estrogen stimulation. Multiple uterine fibroids are one of the special forms of leiomyoma, as it refers to more than one type of myomas taken place in the uterus

which can be subendometrial, intramural, subserosal. It is of high risk of recurrence (Fauconnier, Chapron, Babaki-Fard, & Dubuisson, 2000; Radosa et al., 2014).

Currently the treatment for multiple leiomyomas involve mainly surgical interventions. However, the approach of surgery is largely dependent on the patients' age and will to preserve the fertility. The commonly accepted concept for surgical interventions now is to avoid "radical" surgery such as hysterectomy in order to perseve organ integrity and prevent pelvic organs prolapse. More and more gynecologists also realized that preserving the uterus can help protecting the blood supply for the ovaries and therefore preserving the ovarian function. Therefore, myomectomy by either hysteroscopy or laparoscopy has become the dominant choice. However, it is widely known that the recurrence rate for leiomyoma after myomectomy can be as high as 60% after 5 years (Donnez, Donnez, & Dolmans, 2014; MALONE, 1969). As for multiple leiomyomas the recurrence is even higher (MALONE, 1969).

Since the growth of leiomyoma is heavily influenced by estrogen level, gonadotropin-releasing hormone agonist (GnRHa) was first investigated as a potential treatment since 1980s. It is confirmed that GnRHa can decrease the volume of fibroid and uterus (Falsetti, Mazzani, Rubessa, & Ruggeri, 1992; Jasonni et al., 2001). Currently GnRHa has been used pre-operationally as it can decrease the pre-operative and perioperative blood loss therefore improves the condition of the surgery (Zhang et al., 2014). However, there is lack of clinical trials looking into the agents of preventing recurrence of the multiple leiomyomas after conservative surgery..

At present, there is no guideline for the long term management in multiple leiomyomas. A randomized trial is warranted to test the efficacy of the GnRHa in the prevention of the recurrence of the multiple leiomyoma. This study is a multicenter randomized controlled trial comparing the efficacy of GnRHa with observation in recurrence prevention among women had myomectomy.

Methods

This study is designed to compare the recurrence rate of leiomyomas after myomectomy treating with or without GnRHa.

Study population

This study is conducted in 12 acedemic hospital locatated in central China.

Inclusion criteria

The inclusion criteria are as follows:

1. Women aged ≥18 and ≤45 years;
2. Women who are diagnosed with multiple leiomyomas,which is more than one type of leiomyomas taken place in the uterus, including subendometrial, intramural and subserosal leiomyoma;
3. Women who undergo myomectomy and are confirmed leiomyoma by pathology lab;

4. Ultrasound confirms no fibroid left or the diameter of the fibroid is smaller than 2cm one month after the surgery;
5. Women who don't used medications for leiomyoma 3 months before the enrollment;
6. Women who can give written consent

Exclusion criteria

The exclusion criteria are as follows:

1. Women who have been diagnosed with congenital uterine abnormalities such as uterine malformation (uterus unicornis, septate uterus, or duplex uterus);
2. Women who are pregnant;
3. Women who are diagnosed with other estrogen dependent diseases such as adenomyoma or endometriosis;
4. Women who have used GnRHa three months before enrollment;
5. Women with medical conditions that contraindicate surgery, such as uncontrolled hypertension or known symptomatic heart disease; poorly controlled type 1 or type 2 diabetes mellitus; undiagnosed liver disease or dysfunction (based on serum liver enzyme test results); renal disease or abnormal serum renal function; severe anemia; history of deep venous thrombosis, pulmonary embolus, or cerebrovascular accident; history of (or suspected) cervical carcinoma, endometrial carcinoma, or breast carcinoma;
6. Women who are allergic to the GnRHa;
7. Women who are also undertake other clinical trials at the same time.

Study intervention

Myomectomy

Myomectomy is performed in patients who are suspected to have multiple leiomyomas. Myomectomy can be conducted by laparoscopic, hysteroscopic or abdominal approach. The length of the surgery, numbers and size of the fibroids, blood loss and the integrity of the uterine cavity should be kept in record.

Screening

At the screening visit, previous medical history and current medication status are reviewed with the standardized case report forms. The multiple leiomyomas is confirmed by the pathology lab report.An imaging such as transvaginal ultrasound scan or MRI are performed one month after the surgery. Laboratory measurements including basal sex hormone tests, AMH, safety assays such as liver function, renal function, hepatitis virus, HIV, syphilis, coagulation, blood routine, and urine routine are performed in

the local labs of the study sites. Quality of life is recorded using the SF-36 and pictorial blood loss assessment chart, PBAC.

Enrollment

Written informed consent will be obtained from the patients after discussion.

Randomization and safety

Simple randomization is used to assign subjects to two groups with a 1:1 ratio. The randomization is stratified by study site. The sequence of randomization has been generated by biostatisticians in data coordinator center with Microsoft excel. 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 online 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. All potential adverse events will be monitored throughout the trial, with the supervision from the Huazhong University of Technology and Science Ethnic committee. Participants can quit the trial anytime when there is intolerance of the therapy or serve side effects.

The intervention

Participants in the treatment group will receive a dose of 3.75mg of gonadotropin-releasing hormone agonist (GnRHa) intramuscular injection (Diphereline, Ipsen, France) day one of the menstruation after the surgery. The intervention will repeat monthly for 6 months. Hypogonadic side effects caused by medication such as hot flushes, bone loss should be carefully evaluated and could be treated with add-back therapy to maintain estradiol at the level of 30-50 pg/ml.

A schedule of enrollment, interventions, and assessment is provided as in the table below (Table. 1). The flow chart of this study is given in Fig. 1.

Follow up observations

There are seven followups after the surgery, every three months in the first two visits and every six months in the following visits. During each visit, the sex hormones, AMH is tested and the pelvic ultrasound is prescribed. The SF-36/PBAC is also recorded.

The patients can quit the trial when the side effects of the medication is unbearable or they are not willing to participate and a ITT analysis will be performed including these patients. The trial should immediately stop when there is any adverse events. Adverse events are any unfavorable medical occurrences associated with the subject’s participation in the research, whether or not considered related to the study intervention.

Outcomes and outcome assessments

The primary outcome is recurrence. The secondary outcomes include uterine size, menstruation blood loss, clinical pregnancy, ovarian reserve, quality of life and other adverse events. Regarding recurrence, it defines as the recurrence of symptoms or the growth of fibroids. The symptoms refers to increased menstruation blood loss (PBAC larger than 100). The growth of fibroids is defined as the diameter of the fibroid larger than 2cm or the number increased compared to the baseline image one month after the surgery.

Data analysis

Sample size calculation

Based on the retrospective data from our department, the recurrence rate of multiple leiomyomas 3 years after the surgery is about 30%. It was assumed that an absolute difference of 10% in recurrence rate will be of clinical significance. We aim to test a difference of 10% of recurrence rate between treatment and observation groups (i.e., 20% in the GnRHa group and 30% in the observation group) at a significance level of 0.05 with a statistical power of 80%. The minimal sample size calculated is 291 for each group. In consideration of a dropout rate of 10%, we will enroll 320 subjects in each group.

Data collection

Patient will be recruited from March 2018 to March 2020, and follow up will be done three years after the surgery. 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.

Data analysis

Data analysis and reporting will be conducted in accordance to the CONSORT guideline, which were recorded in our flow chart (Fig 1), including the number of eligible participants and lost to follow-up for various reasons.

Intention to treat will be used as a foundation in our analysis. Comparisons of the characteristics at baseline will be carried out 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 two groups after three years' follow-up, which will be analyzed by Pearson chi-square test. For efficacy parameters, such as score of menstruation blood loss, size of uterus and lesion will be analyzed using generalized estimating equations (GEE) to account for correlations among these observations in different follow up points.

The parameters from secondary outcomes contains SF-36 score, PBAC score are calculated during three years' follow-up are using mixed effects model repeated measures (MMRM) analysis to compare differences between two groups at different time points.

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

Discussion

This is a study comparing the efficacy of GnRHa with observation in women who have had myomectomy for multiple leiomyomas. We plan to enroll 640 subjects from 12 teaching hospitals in China. The enrollment began in March 2018.

At the time of manuscript preparation, more than 270 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 multiple leiomyomas after myomectomy.

Currently the treatment for leiomyoma is largely rely on surgery, while hysterectomy is more radical it can also cause more complications in short and long term. Myomectomy on the other hand, can preserve the integrity of the uterus ("ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas," 2008) while the recurrence is as high as 30% three years after the surgery. Second surgery would be more difficult because of the iatrogenic adhesion and sometimes hysterectomy is inevitable. The etiology of leiomyoma is still not fully understood, however epigenetic and metabolic abnormalities are identified in a large percentage of the leiomyoma (Holdsworth-Carson, Zaitseva, Vollenhoven, & Rogers, 2014; Medikare, Kandukuri, Ananthapur, Deenadayal, & Nallari, 2011). These could be of potential value for the development of new therapeutic strategies (Commandeur, Styer, & Teixeira, 2015). Medications for leiomyoma are mostly based on hormone modulation, such as selective progesterone receptor modulators (SPRMs), GnRHa and combined contraception pill (COP). While COP is contradicted in women aged more than 40, the effectiveness of SPRMs versus other treatments is also not clear (Murji, Whitaker, Chow, & Sobel, 2013). GnRHa was firstly used in treating leiomyoma since 2010 and it has been confirmed that preoperative GnRHa can significantly reduce uterine and fibroid volume (Lethaby, Puscasiu, & Vollenhoven, 2017). However, there is lack of clinical trial investigating the effect of GnRHa in preventing the recurrence of leiomyoma after myomectomy.

At present, the long-term management of leiomyoma lacks of a standard guideline. This study is expected to provide a reliable answer to that whether GnRHa can protect recurrence of multiple leiomyomas.

Trial Status

The enrollment of this study is ongoing at the time of manuscript submission. The trial was registered in Chinese Clinical Trial Registry, ChiCTR-IPR-17012992 (http://www.chictr.org.cn/showproj.aspx?

proj=21797) on 15 Oct 2017. The protocol version number is v.1.0 (Nov-10-2017) and the recuitement date is March-15-2019 and it will take approximately 2 years to complete the recruitment.

Declarations

Ethics approval and consent to participate

The experiments “GnRHa vs. observation in the treatment of multiple leiomyomas after myomectomy: study protocol for a multicenter, prospective, randomized controlled clinical trial’ involving randomized clinical trial on human were approved by Medical Ethics Committee of the Tongji Hospital Affiliated to Tongji Medical college of Huazhong University of Science and Technology (TJ-IRB20180311) according to submitted study protocol (Version 1.0, 2017-Nov-10) and informed consent (Version 1.0, 2017-Nov-10). The ethical approval was approved by both central and local levels. Central ethical approval has been confirmed from the Medical Ethics Committee of the Tongji Hospital (ref approval no. TJ-IRB20180311) and we will not begin recruiting at other centres in the trial until local ethical approval has been obtained.

Consent for publication

Not applicable

Availability of supporting data

All data generated or analysed during this study are included in this published article

Competing interests

All authors declare no compete of interests.

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Authors' contributions

All authors were invlolved in the study design. Jia Wei and Xiangyi Ma comtrisbute to data collection and trial progress management. Wenwen Wang and Minli Zhang are responsible for the data analysis, Zhiying Yu, Wei Zhang, Li Hong, Zhiying Li, Lin Li, Yan Wang, Yun Feng, Ruixia Guo, Chunlian Zhang, Qingfen Yue and Wuliang Wang were in charge for the participants recruitment in different centres, Shixuan Wang was responsible for the whole trial management.

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Tables

Table 1. Schedule of enrollment, intervention and assessment

	STUDY PERIOD (months)									
	Enrolment	Allocation	Post-allocation							Close-out
TIMEPOINT**	*-1*	0	*3*	*6*	*12*	*18*	*24*	*30*	*36*	*36*
ENROLMENT:										
Eligibility screen	X									
Informed consent	X									
Allocation		X								
INTERVENTIONS:										
GnRHa										
Observation										
ASSESSMENTS:										
Ultrasound/MRI	X		X	X	X	X	X	X	X	
SF-36/PBAC			X	X	X	X	X	X	X	
FSH, E2, AMH			X	X	X	X	X	X	X	

Figures

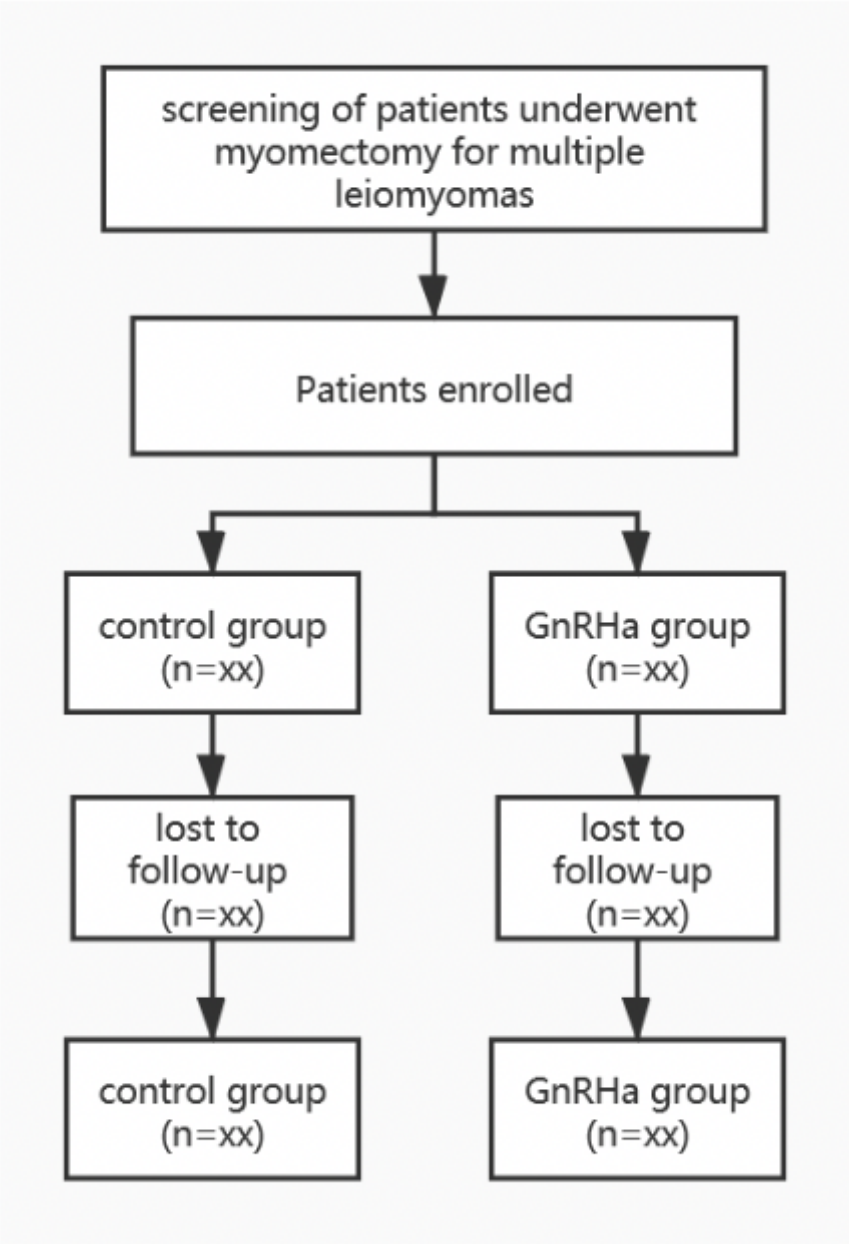

Figure 1

The flowchart of the studyThe flowchart of the study

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