Contemporary Clinical Trials Communications 34 (2023) 101179

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

The efficacy of GnRH-a followed by SanJieZhenTong capsules in long-term management of endometriosis: Study protocol for a multicenter, double-blinded, double-dummy randomized clinical trial

Yunxi Zheng [a,b,c,1], Ruoyi Guo [a,b,c,d,1], Qi Tian [a,b,c], Yan Du [e], Li Wang [a,b,c,d], Zhiling Zhu [a,b,c,d], Erkai Yu [f], Jing Sun [g,1,**], Xiaofang Yi [a,b,c,*,1], Congjian Xu [a,b,c,***,1]

[a] Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, 200011, China
[b] Department of Obstetrics and Gynecology, Shanghai Medical School, Fudan University, Shanghai, 200011, China
[c] Department of Gynecology, Shanghai Key Laboratory of Female Reproductive Endocrine-Related Diseases, Shanghai, 200011, China
[d] Department of Integrated Traditional & Western Medicine, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, 200011, China
[e] Office of Clinical Epidemiology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China
[f] Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, 200011, PR China
[g] Department of Obstetrics and Gynecology, Shanghai First Maternity and Infant Hospital, Shanghai, 200011, PR China

ARTICLE INFO

Keywords:
Endometriosis
Traditional Chinese medicine
Randomized controlled trial
Long-term management
Recurrence

ABSTRACT

Background: Endometriosis is a common benign gynecological disorder with high risk of recurrence and adverse impact on fertility-sparing. This study aims to evaluate the effectiveness and safety of SanJieZhenTong Capsules, a traditional Chinese medicine, in the long-term management of endometriosis postoperatively.

Methods: and analysis: A prospective, double-blinded, double-dummy parallel-group randomized controlled trial will be conducted at three university-based medical centers in China. A total of 600 patients with rAFS III-IV endometriosis diagnosed by laparoscopy will be enrolled. After fundamental treatment (gonadotropin-releasing hormone agonists injection starts on the first day of menstruation postoperatively, and repeats 3 times every 28 days), participants will be randomly allocated to the oral contraceptive group (oral contraceptive + dummy A) or SanJieZhenTong Capsules group (SanJieZhenTong Capsules + dummy B) in a 1:1 ratio. All participants will be treated and followed up for 52 weeks. The primary outcome is a recurrence rate based on endometriosis-related symptoms, physical examination, and/or ultrasound/MRI findings. The secondary outcome includes changes in quality of life and organic function outcome via the 36-item Short-Form scores and gastrointestinal function score.

Conclusion: The current trial could provide rigorous evidence on SanJieZhenTong Capsules application in the long-term management of advanced-stage endometriosis.

1. Background

Endometriosis is defined as the presence of endometrium-like tissue outside the uterine cavity, which affects more than 10% of reproductive-age women. Till 2020, the accumulated number of patients has been over 190 million worldwide [1]. Most patients suffer from infertility and a collection of chronic pain symptoms, including dysmenorrhea, deep dyspareunia, dyschezia, and gastrointestinal disorders such as irritable

Abbreviations: RCT, randomized controlled trial; GnRH-a, gonadotropin-releasing hormone agonists; OCs, oral contraceptives; TCM, traditional Chinese medicine; SZC™, SanJieZhenTong capsule; PCOS, polycystic ovary; QoL, quality of life; SF-36, 36-item Short-Form; SAE, serious adverse event; CRF, case report form; CRC, clinical research coordinator; AE, adverse event; VAS, visual analogue scale; GIQLI, gastrointestinal quality of life index; LARS, low anterior rectal resection syndrome scores; CRADI-8, colorectal anal distress inventory 8; AMH, anti-Mullerian hormone; FSH, follicle stimulating hormone; E2, estrogen; ITT, intention-to-treat.

* Corresponding author. Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, 200011, China.
** Corresponding author. Department of Obstetrics and Gynecology, Shanghai First Maternity and Infant Hospital, Shanghai, 200011, PR China.
*** Corresponding author. Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, 200011, China.
E-mail addresses: sunjing61867@tongji.edu.cn (J. Sun), yix@fudan.edu.cn (X. Yi), xucongjian@fudan.edu.cn (C. Xu).
[1] contributed equally.

https://doi.org/10.1016/j.conctc.2023.101179
Received 13 April 2023; Received in revised form 15 June 2023; Accepted 19 June 2023
Available online 20 June 2023

bowel syndrome, which seriously affect the patient's quality of life [2].

Surgery was once been recognized as the "first line" and "golden standard" for the treatment of endometriosis, however, it's estimated that without further medical treatment, the recurrence rate could be up to 50% within 5 years postoperatively [3]. Recurrence is a great challenge for gynecologists, and previous research has proved recurrent endometriomas may decrease the fertile capability significantly [4,5]. A prospective randomized controlled trial (RCT) of 450 patients with endometriosis showed that the recurrence of dysmenorrhea and dyspareunia was lowest in patients who received combined treatment (surgery followed by 3-month hormone therapy) than that of hormone therapy or surgery therapy alone [6]. Therefore, long-term management after endometriosis-related surgery is necessary. Current medical treatments mainly refers to hormonal treatment. Although gonadotropin-releasing hormone agonists (GnRH-a), oral contraceptives (OCs), and progesterones are effective [7–9], the hypoestrogenic affects, potential irregular bleeding and amenorrhea limit the long-term patients' compliance. our previous clinical trial had already demonstrated that Traditional Chinese Medicine (TCM) features mild reaction, and few hormone-related side effects were reported [13].

Till today, there's no consensus of medical application has been reached, nor guidelines of adjuvant medical treatment for those who are contraindicative to hormone therapy. The ideal long-term management regimen should be cost-effective, well-tolerated, and without significant adverse effects on patients. SanJieZhenTong capsule (SZC™), a TCM, is made of four herbs: Resina Draconis, Panax Notoginseng, Bulb of Thunberg Fritillary, and Coicis Semen. Published research has revealed that SZC™ is effective to reduce endometriotic lesions in rats [10,11]. Our preliminary study showed that SZC was more effective in relieving pain and improved quality of life (QoL) with fewer adverse events in patients with moderate-to-severe EMs than a GnRH-a or OCs [13]. Although Chinese herbal medicine is widely used and gradually becomes the alternative treatment of endometriosis in clinical due to the less contraindications and side effects and has little impact on menstrual cycle, few rigorous studies were reported under peer review. As of October 25, 2012, 35/71 endometriosis-related interventional trials registered with ClinicalTrials.gov have been completed. Of these 35, only 11 (31.4%) had published results [12]. It is possibly due to a lack of efficacy, safety problems, or both, especially, for TCM. Poor repeatability and non-compliance with international standards of research have seriously restricted the objective evaluation of the efficacy of Chinese medicine by the international community.

Therefore, it's urgent to carry out high-quality research to assess the effects of SZC™ on the long-term management of endometriosis compared to "first-line" hormone therapy. In the current study, we designed a prospective, randomized, double-blinded, double-dummy, parallel-group clinical trial with a multicenter involved to investigate the effects of SZC™ for recurrence prevention and organic function preservation.

2. Methods

2.1. Study design

The current clinical trial is a prospective, randomized, double-blinded, double-dummy trial. The study protocol has been registered at the Chinese Clinical Trial Registry, http://www.chictr.org.cn/, with the registry number: ChiCTR1900027189. The registration date was Nov 4th, 2019. Followed by guidelines of Standard Protocol Item Recommendations for Interventional Trials (SPIRIT), recruitment from three university-based medical centers, including Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China (OBGYN-FU); Shanghai First Maternity and Infant Hospital affiliated to Tongji University, Shanghai, China (SFMIH-TU); and Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China (LH-TCMU). Under the approval of the Ethics Committee of the Gynecological and Obstetrics Hospital of Fudan University (2020-137) and the other two joint centers, the recruitment began on Jan 2nd, 2021. Patients who surgically confirmed the diagnosis of severe endometriosis will be enrolled in three medical centers. After fundamental treatment for 3 cycles of GnRH-a injections, patients will be randomly allocated to SZC™ or OCs group (Fig. 1).

GnRH-a: gonadotropin-releasing hormone agonists; SZC™: SanJieZhenTong Capsule; OCs: oral contraceptives; SF-36:36-item Short-Form.

2.2. Study population

Eligible participants will be recruited from three medical centers. Patients will be enrolled for further screening according to the inclusive and exclusive criteria. After face-to-face communication with principal investigators, detailed information including interventions, long-term assessments, benefits, and potential adverse reactions will be fully announced. Written informed consent will be obtained after full consideration from all participants before their participation.

2.3. Inclusive criteria

(1) age ranges from 18 to 45 years old;
(2) patients received conservative surgery for endometriosis at the above-mentioned three medical centers;
(3) endometriosis of stage III-IV (according to rAFS criteria);
(4) without a birth plan within one year;
(5) physical and mental health to ensure correct expression of complaints and symptoms;
(6) informed consent was signed.

2.4. Exclusive criteria

(1) patients who suffer gynecologic malignant tumor malignancies, genital tubercle;
(2) patients who had undergone total hysterectomy with bilateral salpingo-oophorectomy;
(4) patients suffered other internal diseases, like cardiovascular, hepatic, renal, or hematopoietic disease;
(5) patients accompanied by other gynecological endocrine diseases, such as polycystic ovary (PCOS).
(6) pregnancies or willing to be pregnant in 1 year;
(7) patients who are allergic to the experimental drugs; or those who have participated in other clinical trials;
(8) Hb < 80 g/L;
(9) stage I and II of endometriosis;
(10) with a family history of thrombosis or thrombotic disease.

2.5. Sample size

The Sample size is based on the recurrence rate of endometriosis postoperatively, with the following formulation (Fig. 2). According to a previous preliminary study, the estimated recurrence rate was about 10% after medical treatment of SZC™ [13] and about 20% after receiving OCs in 2 years [14]. In the current study, we assume the type I error probability level α of 0.05 and power (1-β) of 0.9. Taking account of the 10% dropout rate, a total of 600 participants should be recruited (300 patients per treatment arm).

The type I error probability level α of 0.05, Z value is bilateral, $Z\alpha = 1.96$. With the power (1-β) of 0.9, $Z\beta = 1.28$. P1 and P0 represent recurrence rates after medical treatment of SZC™ or OCs, which was 10% and 20%, respectively. P represents the mean value of P1 and P0.

2.6. Randomization and allocation

The study uses the block randomization method. All participants are

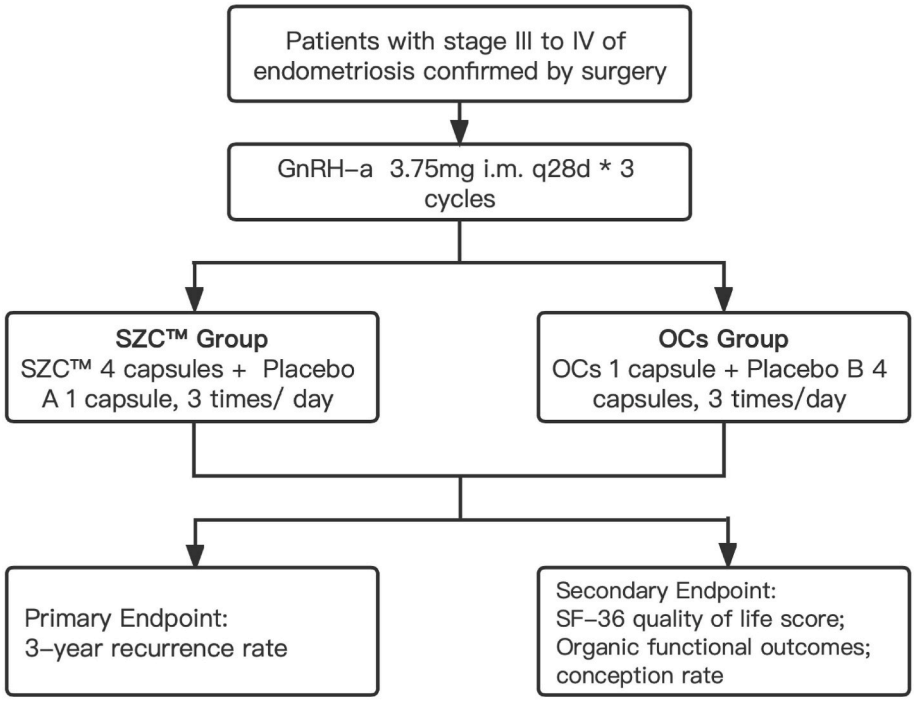

Fig. 1. Flow chart of this study.

$$N = \frac{(Z_\alpha + Z_\beta)^2 \times \bar{P}(1-\bar{P})}{(P1 - P0)^2}$$

Fig. 2. Illustrates the sample size scheme for each arm.

cluster randomly assigned to SZC™ or OCs group, in a 1:1 allocation (each group n = 300, expected) via a randomization procedure implemented with the Data Acquisition and Processing (DAP) Electronic Data system (EDC V5.0; https://www.nextedc.cn/) after signing the informed consent form. The randomization process was blinded to the data management and the statistical analyst. The random code was randomly generated by computer software and stored in the Gynecological and Obstetrics Hospital of Fudan University (researcher) in paper form.

The drug package numbers were generated on Jan 15th, 2021, through central randomization and drug management system software (Randomization and Trial Supply Management system, RTSM), DAP. The number in the SZC™ group and OCs group were equal. The RTSM generated a random block allocation sequence to assign drugs to the participant, with each participant receiving an individual package of the drug from each center. The drug package number and verification code information shall be registered and stored in the RTSM system after the blind coding on-site for drug distribution.

2.7. Blinding

The randomization sequence will be blinded to either the recruitment of participants or the investigators. The dummy of SZC™ or OCs looks the same as SZC™ or OCs. After checking the appearance and properties of the drugs and dummies, the third-party staff will distribute the packaging according to a random number. Any serious adverse event (SAE) will lead to unblinding.

2.8. Interventions

All included patients were given fundamental treatment in the first stage. On the 1st of menstruation post-operatively, GnRH-a will be given. A total of 3 times GnRH-a will be injected with the interval of 28 days. During the first stage, estrogen will be monitored, and "add-back" therapy will be given if required. Twenty-eight days after the last injection of GnRH-a, eligible patients will be allocated into 2 groups randomly:

(1) SZC™ group: SZC™ 4 capsules*3 times/a day + dummy A 1 tablet*once/a day
(2) OCs group: dummy B 4 capsules*3 times a day + Drospirenone and Ethinylestradiol Tablets (II) 1 tablet*once/a day.

Both dummy A and dummy B are similar to real drugs in color, taste, and smell. The medical treatments in the current study will last 52 weeks for all patients.

2.9. Visit schedule

All participants receive the initial visit after the completion of screening, and each participant will be identified by a specific ID number. A case report form (CRF) will be established, and clinical research coordinator (CRC) will help monitor the follow-up visit schedule. Besides baseline visits, patients will attend 52 weeks of follow-up visits scheduled on 3, 6, 12, 18, and 24 and 36 months ±7 days postoperatively. A full-time CRC was equipped to confirm the adherence, and the rate of lost-to-follow-up would be calculated. Lost to follow-up is defined as any loss of follow-up visit within the scheduled period for any reason. At the baseline visit, personal characteristics, surgical information, assessment of the quality of life (QoL), fertility history, endometriosis-related pain, and symptoms will be collected. In the follow-up visits, we will record QoL and endometriosis-related symptom scales, and AE (adverse events) data by the detailed visit schedule (Table 1).

Table 1
visit schedule for the clinical trial.

Procedure	Screening (Baseline)	Post-treatment follow-up (1 month)	3-month	6-month	12-month	18-month	24-month	36-month
Informed consent	✓							
Inclusion and exclusion	✓							
Medical history	✓							
blood test	✓	✓	✓	✓	✓	✓	✓	✓
Randomization	✓							
GnRHa injection		✓	✓					
Treatment/placebo dispensed			✓	✓	✓	✓	✓	✓
Concomitant medication collection				✓	✓	✓	✓	✓
Participants electronically fill out questionnaires	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events		✓	✓	✓	✓	✓	✓	✓
Dispense/return study drug				✓	✓	✓	✓	✓

2.10. Discontinuation

In case of the following emergencies, participants will be allowed to discontinue and withdraw from the current study:

(1) allergic reactions or serious adverse events that should be withdrawn according to the physician's judgment;
(2) Poor compliance;

Patients will be advised to contact their doctors in the event of any undesirable effect after the application of SZC™ or OCs treatment. For those who discontinued the clinical trial, the gynecologist in charge will continue to provide professional treatment for the patients, and a long-term follow-up visit will still be carried out as scheduled.

2.11. Primary outcome

The primary outcome for the current study is the recurrence rate in 3 years postoperatively. Recurrence can be divided into three types: (1) symptomatic recurrence, which is defined as a reappearance of clinical symptoms, including dysmenorrhea, dyspareunia, and defection pain. Quantitatively, visual analogue scale (VAS) scores should reach the level before treatment, or higher; (2) recurrence confirmed by physical examination: pelvic adhesion, ovarian mass, and/or tenderness nodules in the posterior pelvis is detected; (3) recurrent endometriotic lesion detected by ultrasound/MRI examination [15].

Recurrence will be confirmed after ruling out the following situations:1) symptom persistence: endometriosis-related symptoms persist for more than 3 months after the surgery; 2) new onset of symptoms, which is defined as new appearance of endometriosis-related symptoms after the operation.

2.12. Secondary outcomes

(1) Changes in quality of life, as measured with 36-item Short-Form (SF-36). The questionnaire includes eight sessions: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), Vitality (VT), social functioning (SF), role emotional (RE), mental health (MH) [16].
(2) Changes in organic function. Questionnaires of GIQLI (gastrointestinal quality of life index), Wexner incontinence/constipation score, LARS (low anterior rectal resection syndrome scores), and CRADI-8 (colorectal anal distress inventory 8) are used to assess rectal function. Sexual function is assessed via FSFI (Female Sexual Function Index) questionnaire. Ovarian function evaluation will be carried out by KI (Kupperman index) questionnaire, and AMH (anti-Mullerian hormone), FSH (follicle stimulating hormone), and estrogen (E2) levels via blood test [13,16–23].

2.13. Data management

A certain professional gynecologist will be responsible for patients' recruitment, medical treatment, and long-term follow-up in each medical center. The CRC will help with regular contact with patients, distribute medicines, and record information on baseline and follow-up visits. Original data from clinical assessments and patient surveys will be captured electronically in the Data Acquisition and Processing Electronic Data system (DAP-EDC, V5.0). The research manager will monitor the clinical data once a week. Signed consent forms and paper copies of source documentation will be securely held on the study team database, accessible only by authorized investigators to monitor. The final dataset will only be accessed by the specific statistical analyst.

2.14. Quality control

To ensure the high quality of the trial, all staff will receive strict training before baseline data acquisition to guarantee consistent practices. The training includes unifying surgical procedures, recruiting patients, and completing and uploading CRFs.

Dropouts and withdrawals from the trial will be recorded to ensure an intention-to-treat (ITT) analysis. In addition, an independent data and safety monitoring team will be established to identify problems and monitor and check the collected data. Staff will review the data once a week and have the authority to suspend at any time if they discover a problem or adverse event during the trial.

Adverse symptoms related to medical usage will be defined as AE, which should be reported to the Ethics Committee immediately and will be regularly monitored at every follow-up visit. Additionally, regular liver function, kidney function, routine blood tests, and coagulation function as safety markers will be checked every 6 months postoperatively, to exclude severely impaired physical function and evaluate the possible side effects. Those fatal, life-threatening events will be confirmed as SAEs. Any SAEs will be reported to the chief Investigator and reported to relevant authorities immediately. After professional evaluation, patients should be asked to quit the clinical trial and medical treatment will be revealed.

Any changes to the study protocol are provided to the Ethics Committee of the Gynecological and Obstetrics Hospital of Fudan University as per protocol.

2.15. Statistical analysis

Baseline demographics will be reported using descriptive statistics. Since this study is a multicenter clinical trial, the influence of the central effect on efficacy indicators should be considered in the analysis. The analysis of covariance or Wilcoxon rank sum test with consideration of central factors was used for the measurement data, and the CMH (Cochran-Mantel-Haenszel) chi-square test with the correction of the center was used for the count data. All scores will be analyzed using

repeated measures via generalized estimating equation (GEE) model analysis of variance with time. For <5% loss to follow-up, a complete case analysis will be done. For >5% loss to follow-up, multiple imputations and complete case-sensitivity analyses will be done.

Statistical analyses were carried out using the software SPSS v26. Statistical significance will be set at $P < 0.05$.

2.16. Ethics and dissemination

This study was approved by the Ethics Committee of the Gynecological and Obstetrics Hospital of Fudan University (2020-137) and the other two joint centers. All participants will provide written informed consent before randomization. The results of this research will be presented at academic conferences and peer-reviewed journals.

3. Discussion

TCM is commonly recommended by Chinese medicine practitioners and has been promoted worldwide [24]. Though SZC™ is commonly used in the treatment of endometriosis, the evidence of effectiveness for herbal medicine is limited. This randomized clinical trial will help in understanding the efficacy and safety of SZC™ in the long-term management of endometriosis.

To erase the subjective impact on results assessment, all patients and staff included in this study are blind to the treatment groups. We also prepare dummies to modify the shape, taste, and smell of the real drugs. Evaluation of randomized samples will improve the reliability of the results as well. Meanwhile, a multicenter-involved, prospective clinical trial will make it possible to reduce potential bias.

Recurrence and fertility preservation are troublesome issues both for gynecologists and patients. Besides the re-occurrence of endometriosis lesions via ultrasonic and radiological examination, symptomatic recurrence is much more common. In our study, the primary endpoint is to evaluate the capability of recurrence prevention. Changes in rectal and sexual function, quality of life, and pain control will be also assessed as secondary endpoints. Previous studies have investigated the effects of SZC™ on reliving endometriosis-related pain and improving fertility outcomes [13,25], the current study will allow us to determine the efficacy and safety of long-term management for endometriosis.

According to guidelines for the treatment of endometriosis in China, long-term management has reached a consensus. Hormone therapy is regarded as the first-line maintenance treatment for endometriosis, but TCM hasn't been widely promoted [26]. If the RCT could prove the efficacy of SZC™ in the long-term management of endometriosis, it'll be possible to formulate guidelines for integrated traditional Chinese and Western medicines for moderate and severe endometriosis.

This is the first study to be carried out to determine the efficacy of TCM (SZC™) on the long-term management of endometriosis. The scientific design which is following modern trends will help make a solid conclusion. Besides the limitation of sample size and biases, the proposed study will provide valuable information to expand medical choices for the long-term management of endometriosis, especially for those who are contraindicated to hormone treatment. If the favorable result is proven, SZC™ is expected to be widely promoted to prolong the recurrence-free interval, and to reduce the burden on endometriosis patients and the healthcare system.

Trial status

The RCT is in progress and recruiting endometriosis patients. The protocol version is 1.0 and was updated on Oct. 25th, 2021. The enrollment of the current study will be conducted till December 2023.

Funding

This study was supported by the following foundational grants: Shanghai Shen Kang Hospital Development Center (SHDC12019106).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgment

All authors discussed and helped to improve the protocol, and read and approved the final manuscript. Yunxi Zheng, Ruoyi Guo and Qi Tian drafted the manuscript. Yan Du was the epidemiologist of the project. Li Wang, Zhiling Zhu, Xiaofang Yi contributed to enrollment of the patients. Jing Sun, Erkai Yu, and Congjian Xu were the co-PI of the project.

References

[1] A.L. Shafrir, L.V. Farland, D.K. Shah, et al., Risk for and consequences of endometriosis: a critical epidemiologic review, Best Pract. Res. Clin. Obstet. Gynaecol. 51 (2018) 1–15, https://doi.org/10.1016/j.bpobgyn.2018.06.001, 20180703.
[2] T. Falcone, R. Flyckt, Clinical management of endometriosis, Obstet. Gynecol. 131 (2018) 557–571, https://doi.org/10.1097/aog.0000000000002469.
[3] L. Saraswat, D. Ayansina, K.G. Cooper, et al., Impact of endometriosis on risk of further gynaecological surgery and cancer: a national cohort study, Bjog 125 (2018) 64–72, https://doi.org/10.1111/1471-0528.14793, 20170927.
[4] K.T. Zondervan, C.M. Becker, S.A. Missmer, Endometriosis. N Engl J Med 382 (2020) 1244–1256, https://doi.org/10.1056/NEJMra1810764.
[5] P.T.K. Saunders, A.W. Horne, Endometriosis: etiology, pathobiology, and therapeutic prospects, Cell 184 (2021) 2807–2824, https://doi.org/10.1016/j.cell.2021.04.041.
[6] I. Alkatout, L. Mettler, C. Beteta, et al., Combined surgical and hormone therapy for endometriosis is the most effective treatment: prospective, randomized, controlled trial, J. Minim. Invasive Gynecol. 20 (2013) 473–481, https://doi.org/10.1016/j.jmig.2013.01.019, 20130406.
[7] M.A. Bedaiwy, C. Allaire, S. Alfaraj, Long-term medical management of endometriosis with dienogest and with a gonadotropin-releasing hormone agonist and add-back hormone therapy, Fertil. Steril. 107 (2017) 537–548, https://doi.org/10.1016/j.fertnstert.2016.12.024, 20170127.
[8] G.A. Dunselman, N. Vermeulen, C. Becker, et al., ESHRE guideline: management of women with endometriosis, Hum. Reprod. 29 (2014) 400–412, https://doi.org/10.1093/humrep/det457, 20140115.
[9] L. Kuznetsov, K. Dworzynski, M. Davies, et al., Diagnosis and management of endometriosis: summary of NICE guidance, BMJ 358 (2017), j3935, https://doi.org/10.1136/bmj.j3935, 20170906.
[10] J. Zou, Z. Guan, W.Y. Zhang, et al., Beneficial effects of the Chinese herbal medicine Sanjie Zhentong Capsule on experimental endometriosis in rats, Chin. J. Nat. Med. 11 (2013) 666–672, https://doi.org/10.1016/s1875-5364(13)60077-1.
[11] L. Du, D.H. Du, B. Chen, et al., Anti-inflammatory activity of sanjie zhentong capsule assessed by network pharmacology analysis of adenomyosis treatment, Drug Des. Dev. Ther. 14 (2020) 697–713, https://doi.org/10.2147/dddt.S228721, 20200220.
[12] S.W. Guo, J.L.H. Evers, Lack of transparency of clinical trials on endometriosis, Obstet. Gynecol. 121 (2013) 1281–1290, https://doi.org/10.1097/AOG.0b013e318291f299.
[13] J.Y. Ruan, Y.X. Zheng, Q. Tian, et al., Efficacy and safety of SanJieZhenTong Capsules,a traditional Chinese patent Medicine,on long-term management of endometriosis:A randomized controlled trial, Reprod Dev Med 5 (1) (2021) 15–22, https://doi.org/10.4103/2096-2924.313687.
[14] S.W. Guo, Recurrence of endometriosis and its control, Hum. Reprod. Update 15 (2009) 441–461, https://doi.org/10.1093/humupd/dmp007, 20090311.
[15] J.E. Ware Jr., SF-36 health survey update, Spine 25 (2000) 3130–3139, https://doi.org/10.1097/00007632-200012150-00008.
[16] H. Yu, E.E. Chan, P. Lingam, et al., Index admission laparoscopic cholecystectomy for acute cholecystitis restores Gastrointestinal Quality of Life Index (GIQLI) score, Ann Hepatobiliary Pancreat Surg 22 (2018) 58–65, https://doi.org/10.14701/ahbps.2018.22.1.58, 20180226.
[17] P. d'Avout-Fourdinier, M. Lempicka, A. Gilibert, et al., Posterior rectal pouch after large full-thickness disc excision of deep endometriosis infiltrating the low/mid rectum and relationship with digestive functional outcome, J Gynecol Obstet Hum Reprod 49 (2020), 101792, https://doi.org/10.1016/j.jogoh.2020.101792, 20200519.
[18] Ip Jcy, T.C. Chua, S.W. Wong, et al., Rectal disc resection improves stool frequency in patients with deep infiltrating endometriosis: a prospective study, Aust. N. Z. J.

Obstet. Gynaecol. 60 (2020) 454–458, https://doi.org/10.1111/ajo.13145, 20200311.
[19] T.B. Omotosho, A. Hardart, R.G. Rogers, et al., Validation of Spanish versions of the pelvic floor distress inventory (PFDI) and pelvic floor impact questionnaire (PFIQ): a multicenter validation randomized study, Int. UrogynEcol. J. Pelvic Floor Dysfunct. 20 (2009) 623–639, https://doi.org/10.1007/s00192-008-0792-7, 20090212.
[20] T. Juul, N.J. Battersby, P. Christensen, et al., Validation of the English translation of the low anterior resection syndrome score, Colorectal Dis. 17 (2015) 908–916, https://doi.org/10.1111/codi.12952.
[21] E. Garavaglia, A. Inversetti, S. Ferrari, et al., Are symptoms after a colorectal segmental resection in deep endometriosis really improved? The point of view of women before and after surgery, J. Psychosom. Obstet. Gynaecol. 39 (2018) 248–251, https://doi.org/10.1080/0167482x.2018.1445221, 20180308.
[22] E.F. Cruz, V.J. Nina, E.D. Figuerêdo, Climacteric symptoms and sexual dysfunction: association between the blatt-kupperman index and the female sexual function index, Rev. Bras. Ginecol. Obstet. 39 (2017) 66–71, https://doi.org/10.1055/s-0037-1598603, 20170303.
[23] R. Rosen, C. Brown, J. Heiman, et al., The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function, J. Sex Marital Ther. 26 (2000) 191–208, https://doi.org/10.1080/009262300278597.
[24] C. Fisher, J. Adams, L. Hickman, et al., The use of complementary and alternative medicine by 7427 Australian women with cyclic perimenstrual pain and discomfort: a cross-sectional study, BMC Compl. Alternative Med. 16 (2016) 129, https://doi.org/10.1186/s12906-016-1119-8, 20160518.
[25] H.Y. Wang, X.H. Bao, J.F. Dai, [Treatment of ovarian cyst after ovulation-induction with sanjie zhentong capsule], Zhongguo Zhong Xi Yi Jie He Za Zhi 28 (11) (2008) 1026–1028, https://doi.org/10.3321/j.issn:1003-5370.2008.11.019.
[26] A. Flower, J.P. Liu, G. Lewith, et al., Chinese herbal medicine for endometriosis, Cochrane Database Syst. Rev. (2012), Cd006568, https://doi.org/10.1002/14651858.CD006568.pub3, 20120516.