Efficacy of intrauterine balloon stent or oral estrogen on prevention of adhesion after transcervical resection of septum in septate uterus: Study protocol for a randomized controlled multicenter study in China

Shan Deng[1], Zichen Zhao[1], Limin Feng[2], Xiaowu Huang[3], Sumin Wang[4], Xiang Xue[5], Lei Yan[6], Baorong Ma[7], Lijuan Hao[8], Xueying Li[9], Lihua Yang[10], Lan Zhu[1]

[1]Department of Obstetrics and Gynecology, National Clinical Research Center for Obstetric & Gynecologic Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China;
[2]Department of Obstetrics and Gynecology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China;
[3]Department of Hysteroscopic Center, Fuxing Hospital, Capital Medical University, Beijing 100038, China;
[4]Nanjing Maternity and Child Health Care Hospital, Jiangsu Province 210004, China;
[5]The Second Affiliated Hospital of Xi'an Jiaotong University, Shanxi Province 710004, China;
[6]Center for Reproductive Medicine, Cheeloo College of Medicine, Shandong University, Shandong Province 250012, China;
[7]Tianjin Central Hospital of Obstetrics and Gynecology, Tianjin 300199, China;
[8]Chongqing Health Center for Women and Children, Chongqing 401147, China;
[9]Hunan Provincial Maternal and Child Health Care Hospital, Hunan Province 410008, China;
[10]Tangshan Maternal and Child Health Care Hospital, Hebei Province 063000, China.

To the Editor: The septate uterus is the most common uterine anomaly and is associated with an increased risk of adverse reproductive outcomes. Transcervical resection of septum (TCRS) is widely performed in patients with adverse reproductive outcomes. The incidence of *de novo* intrauterine adhesions (IUAs) after TCRS is approximately 5% to 25%.[1] Various anti-adhesion methods are widely used in the clinical management of patients with septate uteri, including intrauterine devices, Foley balloons, estrogen, antibiotics, and hyaluronic acid gel. However, insufficient evidence supports or opposes any of these methods (Level C),[2] lacking high-grade evidence.

We designed this multicenter, open-label, randomized controlled trial to investigate the efficacy of the intrauterine balloon stent and estrogen on preventing the development of IUAs after TCRS (ChiCTR2000032061; ChiCTR.org.cn). The primary outcome is the occurrence of *de novo* IUAs confirmed by second-look hysteroscopy. The secondary outcomes include live birth rate (>28 weeks), pregnancy rate, ongoing pregnancy rate, pregnancy loss rate, operation-related complications, and other adverse events. This protocol and other relevant materials were approved by the Ethics Committee of Peking Union Medical College Hospital (PUMCH; No. JS-2268). This study is compliant with the clinical guidelines and regulations for the management of septate uterus.

We will recruit patients from 10 grade A tertiary hospitals (Supplementary Materials, http://links.lww.com/CM9/B873) treating >50% of Chinese patients with septate uteri, and all the surgeons are experienced in hysteroscopic surgery. The inclusion criteria are women who are (1) ≤35 years; (2) nulliparous; (3) diagnosed with septate uterus according to the European Society of Human Reproduction and Embryology/European Society for Gynaecological Endoscopy (ESHRE/ESGE)-2016 classification criteria[3] and agree to receive TCRS monitored by concomitant laparoscopy; and (4) have regular menstrual cycles. The exclusion criteria are women with (1) double cervix and/or vaginal septum; (2) IUAs; (3) a history of metroplasty; (4) severe endometriosis and adenomyosis; and (5) breast cancer.

Recruitment began in May 2020 and is expected to finish by April 2022. Due to the COVID-19 pandemic, recruitment could be prolonged. Informed consent will be obtained from eligible patients by senior doctors at each center.

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Shan Deng and Zichen Zhao contributed equally to this study.

Correspondence to: Prof. Lan Zhu, Department of Obstetrics and Gynecology, National Clinical Research Center for Obstetric & Gynecologic Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China
E-Mail:zhu_julie@vip.sina.com

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This trial was designed as a superiority study. The incidence of postoperative IUAs ranges from 0 to 37.5%, as reported previously.[1,4-6] We selected 24%, 5%, and 5% as the estimated incidence of postoperative uterine adhesion for the control group and two intervention groups, respectively. The required sample size for 80% power using a two-tailed test at $\alpha = 0.05$ was 81 in each group, with an expected dropout rate of 10% (http://powerandsamplesize.com). Therefore, we aim to recruit 243 patients.

Each center will be distributed a target number of participants to recruit. On the day of surgery, the participants will be assigned 1:1:1 to one of the three groups by a central unblocked randomization system on an online platform (http://www.medresman.org). The surgery-only group (Group A) will be the control group without any adjuvant therapy. The participants in the balloon group (Group B) will have an intrauterine balloon stent placed during the operation. The participants in the estrogen group (GroupC) will take estradiol valerate (2 mg, bid) for 2 months after surgery. After randomization, the investigators and the participants will know the specific assignment, while the outcome assessors and data analysts will be blinded.

Before surgery, baseline characteristics will be recorded, including age, gravida, para, menstrual history, body mass index, and some other information. Three-dimensional ultrasound will be carried out to assess the uterine cavity in the coronal position and measure the septum's size [Supplementary Table 1, http://links.lww.com/CM9/B873].

The participants will undergo surgery within 1 week after menstrual bleeding. All the participants will receive a single dose of prophylactic antibiotics, commonly second-generation cephalosporins, within 30 min before surgery. Other antibiotics will be used as appropriate when an allergy to cephalosporin is considered. The polyps found by hysteroscopy will be resected simultaneously. Bipolar energy devices (needle electrode or cutting loop) will be used.

For the participants in the balloon stent group (Group B), the COOK balloon stent (5 mL) will be inserted into the uterine cavity at the end of the operation and removed in an outpatient setting 1 week later. Only the barrier function of the balloon will be used without water injection into the balloon to avoid pressure on the endometrial blood supply. Using bipolar energy instruments requires cervical dilatation to Hegar 9.5–10, which ensures the balloon's placement. No extra antibiotics will be given during the week because short-term balloon indwelling does not increase the infection risk, according to previous experience.

The participants in the estrogen group (Group C) will start to take oral estradiol valerate (2 mg, bid) from the day after surgery. If menstruation-like bleeding occurs, the medication should be stopped for 5 days before resumption. The management of bleeding during medication depends on the specific situation. Progesterone can be added temporarily for bleeding management when there is no sign of ovulation. The investigator will follow each patient's medication use.

Based on our clinical experience, the dosage of estrogen and the COOK balloon stent used in this trial is safe and is probably associated with only slight adverse effects. Anaphylaxis rarely occurs. The researchers will answer the participants' questions within 24 hours over the phone and give guidance. If a participant insists on withdrawing from the study for any reason, her choice will be respected.

The participants will undergo a hysteroscopic re-examination at 2 months after TCRS, before which they will be advised of strict barrier contraception. The duration of 2 months was chosen considering the recuperation of the endometrium after surgery, which takes at least 1 month, thus avoiding the preventive effect of hysteroscopic procedures on the formation of IUAs. Adhesion lysis will be performed after the detection of IUAs, and the type and location of the adhesion will be recorded. If a residual fundal notch is found, it will be measured and recorded. Further septal incision will be performed only if the residual fundal notch is >0.5 cm, considering its possible influence on reproductive outcomes. A COOK balloon stent or estrogen is not allowed to be used during or after the second-look hysteroscopy. If a patient inevitably fails to receive a second-look hysteroscopy on schedule, for example, due to quarantining for COVID-19, the re-examination can be postponed, and the reason should be recorded clearly.

All participants will be followed up for >1 year after the second-look hysteroscopy to collect information on their fertility status and reproductive outcome. During the time, the researchers will provide free consultation on common obstetrical and gynecological symptoms and make a diagnosis when necessary. The management-related medical costs will be at the participant's own expense.

The participants will be contacted every 3 months in the following year, which will be informed at discharge. If a participant fails to respond at the 3-month contact, the staff will make every effort to regain contact with the attempts documented via telephone, e-mail, or a letter to their last known mailing address. Should the participant continue to be unreachable, she will be considered lost to follow-up. These participants will not be withdrawn from the study, and existing data will be analyzed. Any incidents of withdrawal and the reason for it will be documented.

We created a unified case report form (CRF) and a web-based data entry system to facilitate the data collection and track the enrollment status regularly. We cooperated with a third-party data management company to customize a mobile application for data input. The participants' information, added by each center, will be fed back to the organizer regularly by the data platform as needed. The adverse events (AEs) will be recorded in the CRF weekly. The investigator at each center is required to report serious AEs in a timely manner by filling in the Serious Adverse Event Report Form within 24 h of discovery and deciding whether they necessitate a participant's withdrawal from the study. In addition, we will establish a platform for patients' self-reporting. The information collected during the follow-up will be specified by the research team before the study.

Patients' records will be anonymized for privacy. The management of patients' medical records will comply with related regulations. Participant case report forms and source documents will be stored securely at PUMCH. Data will be entered electronically from original study materials into a password-protected file for analysis. The electronically transmitted data will be protected with a password. A dedicated staff member will be responsible for the paper and electronic materials involved in this study, and access to the system will be limited to protect the confidentiality of the information.

The chi-square test will be used to compare the rates of three independent samples. *P* values <0.05 will be considered to indicate statistical significance. All statistical analyses will be performed using Stata software, version 17.0. The interim analyses will be performed after one-third or half of the participants undergo second-look hysteroscopy. To avoid bias caused by the interim results in the following research, specialized statisticians free of clinical work will perform the interim analyses. The interventions we will use in this research are widely applied in clinical practice. Therefore, the possibility of pretermination is slight.

The trial will be performed under the guidance and monitoring of the steering committee. It will be overseen by the protocol committee and data coordination committee, consisting of investigators from different centers. The principal investigator will report the trial's progress to the Institutional Review Board of PUMCH once a year. Training and monitoring will be essential in the implementation of this trial to improve the data quality.

The interim quality-control conference will be held every 6 months to monitor the research progress of each center without data disclosure. The registration forms of screened cases and enrolled participants must be submitted monthly. The electronic information form must be completed within one week after the operation. Each center will intermittently perform spot checks of the electronic medical records and conduct on-site supervision when necessary.

The investigators will allow study-related monitoring, including institutional ethics committee review and regulatory inspection(s), and provide access to relevant data or documents. Any protocol modifications, including changes to the eligibility criteria, outcomes, and analyses, will be reported to the ethical committees in a timely manner and the investigators at each center will be informed by telephone, email, or WeChat groups. If the amendment concerns the participants, the investigators at each center will communicate with the participants enrolled there. The results of this study will be published in international peer-reviewed journals and presented at relevant research conferences.

TCRS is performed in many patients with septate uteri, and some will develop IUAs after surgery. However, there is a lack of high-grade evidence on the efficacy of intra- or postoperative anti-adhesion interventions. This trial aims to examine the efficacy of intrauterine balloon stents and estrogen on the occurrence of IUAs after TCRS.

This study is rigorously designed. The large population in China provides a large pool of potential patients. The results of this trial will provide high-quality evidence to guide clinical practice on the primary prevention of IUAs after TCRS. However, recruitment is challenging due to the low prevalence of septate uterus, infrequent screening among women without reproductive problems, and stringent screening criteria. The possible confounders include (1) the effects of a previous uterine operation on the uterine cavity, such as induced abortion, (2) the morphology of the septum, and (3) the compliance of the patients in the estrogen group. Another limitation is that this study will only test the efficacy of one specific balloon stent (COOK) and one specific dosage of estrogen (4mg/day), without comparison with other appliances or dosages.

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References

1. Yu X, Yuhan L, Dongmei S, Enlan X, Tinchiu L. The incidence of post-operative adhesion following transection of uterine septum: a cohort study comparing three different adjuvant therapies. Eur J Obstet Gynecol Reprod Biol 2016;201:61–64. doi: 10.1016/j.ejogrb.2016.01.039.
2. Practice Committee of the American Society for Reproductive Medicine. Uterine septum: A guideline. Fertil Steril 2016;106:530–540. doi: 10.1016/j.fertnstert.2016.05.014.
3. Grimbizis GF, Di Spiezio Sardo A, Saravelos SH, Gordts S, Exacoustos C, Van Schoubroeck D, *et al*. The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies. Hum Reprod 2016;31:2–7. doi: 10.1093/humrep/dev264.
4. Tonguc EA, Var T, Yilmaz N, Batioglu S. Intrauterine device or estrogen treatment after hysteroscopic uterine septum resection. Int J Gynaecol Obstet 2010;109:226–229. doi: 10.1016/j.ijgo.2009.12.015.
5. Vercellini P, Fedele L, Arcaini L, Rognoni MT, Candiani GB. Value of intrauterine device insertion and estrogen administration after hysteroscopic metroplasty. J Reprod Med 1989;34:447–450.
6. Guida M, Acunzo G, Di Spiezio Sardo A, Bifulco G, Piccoli R, Pellicano M, *et al*. Effectiveness of auto-crosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: a prospective, randomized, controlled study. Hum Reprod 2004;19:1461–1464. doi: 10.1093/humrep/deh238.

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