Trial protocol

Title: Comparison of therapeutic efficacy of three methods to prevent re-adhesion after hysteroscopic intrauterine adhesion separation: a randomized study

Principal Investigator: Xiaomin Zhang, Wei Liu

Start-End Times: January 2016- December 2020

1. Overview

1.1 Background

Intrauterine adhesions (IUA) are also known as Asherman syndrome, stemming from Asherman's systematic description of a series of symptoms of in 1948. IUA usually begins with endometrial damage which may be caused by various factors, and may result in fibrosis, leading to IUA occlusion and clinical symptoms, in which menstrual reduction and secondary infertility are the most common symptoms. Other symptoms include amenorrhea, periodical lower abdominal pain in women of childbearing age, and postmenopausal lower abdominal pain. Factors that induce IUA include uterine procedures (such as uterine curettage, cesarean section, and myomectomy), genital tract infections (such as bacterial vaginitis and mycoplasma infection), and genital tract malformations (including uterine mediastinum). Sanders studies on patients with IUA showed that intrauterine manipulation is a major factor in their pathogenesis, and the increased numbers of induced abortions in recent times has contributed to a rise in IUA cases. The focus of current research is on determining measures to restore the structure and volume of the uterine cavity, prevent uterine wall adhesions, and relieve the clinical symptoms of patients, as measures to improve the reproductive function of women of childbearing age.

1.2 Current Status and Future study

With the development of minimally invasive technology, hysteroscopy has become the latest instrument for the accurate diagnosis of IUA, although other auxiliary

examination methods, such as B-ultrasound and MRI, can improve the detection rate of IUA bands. However, the lack of clear vision of hysteroscopy contributes little to the comprehensive AFS score and further treatment after the detection of IUA. Research on current therapies for IUA focuses on five areas: (I) surgical treatments, such as TCRA under hysteroscopy; (II) prevention of re-adhesion, involving physical interventions such as intrauterine balloon, intrauterine device (IUD), and biological interventions including sodium hyaluronate and amniotic membrane; (III) promotion of endometrial regeneration, including estrogen and progesterone therapy, stem cells and Chinese traditional medicine to induce endometrial regeneration; (IV) anti-inflammatory treatment; (V) postoperative reassessment of TCRA, including non-invasive methods such as MRI and B-ultrasound examination and intrusive methods such as hysteroscopy.

2. Objectives

2.1 Overall

This research aims to study the efficacy of an integrated approach to prevent and treat the recurrence of intrauterine adhesions (IUA) after hysteroscopic adhesiolysis.

2.2 Specific objectives

2.2.1 Evaluation of the effect of intrauterine balloons combined with IUD and IUD alone in preventing re-adhesion.

2.2.2 Whether prolongation of intrauterine Foley balloon placement could improve postoperative intrauterine re-adhesion in patients with moderate and severe IUA, and its effect on menstruation and pregnancy rates.

3. Proposal

3.1 Project contents and key issues to be resolved

3.1.1 Clinical research

From January 2016 to December 2019, IUA patients in the Nantong Maternal and Child Health Hospital would be evaluated. Patients with moderate and severe IUA would be selected and admitted for TCRA treatment, then randomly divided into three

groups.

3.1.2 Economic evaluation

Including establish models and data collection. Based on the previous clinical trial data, the models would be established and adjusted. Collect the data from intrauterine adhesion registration, and incorporate the relevant parameters into the models to simulate the occurrence and development of adhesion registration , and to predict the medium- and long-term screening effect and costs.

Key issues to be resolved in this study:

1.Evaluate and compare the awareness and attitude of intrauterine adhesion screening among different population.

2.How to get more IUA patients to volunteer for the program?

3.How to group eligible patients？

4.Investigate the risk factors, monitor the prognosis and recurrence of intrauterine adhesions (IUA) after hysteroscopic adhesiolysis, and observe the changes. Improve the quality of intrauterine adhesions, and obtain the data of intrauterine adhesions in Nantong Maternal and Child Health Hospital.

3.2 Methods

3.2.1 Design

Randomized-controlled trial

3.2.2 Inclclusion criteria and exclusion criteria

Inclclusion standards：①Patients were 20–35 years old with reduced menstrual volume or amenorrhea symptoms;②Patients with moderate and severe adhesions, according to their AFS score;③The patient had fertility requirements, and IUA were the only infertility factors;④There were no contraindications for the use of hormone drugs or antibiotics;⑤Patients had good compliance and were willing to cooperate with the treatment plan.

exclusion standards：①Those with serious medical and surgical disease affecting analyzing the results;②The use of sex hormones to prompt ovarian function decline;③Reproductive tract inflammation, tuberculosis, tumor, or malformation.

3.2.3 Sample size

A sample size of 27 moderate adhesion participants (9 per group) and 45 severe adhesion participants (15 per group) would be calculated to achieve 80% power. To allow for a 10% -20%attrition rate, we planned to enroll 96 participants (16 per group) .

3.2.4 Clinical research methods

Moderate (48 cases) and severe (48 cases) patients would be randomly divided into Three groups: Group A (IUD, n=16), Group B, (Foley1w+IUD, n=16) and Group C (Foley1M+IUD, n=16). All patients would receive sequential treatment of estrogen and progesterone on the day of operation. Follow-up is performed at 1 and 3 months after treatment of uterine cavity, endometrial thickness, menstruation and pregnancy.

3.2.5 Observation indicators

Outcomes：AFS scores、the adhesion type and area、menstrual status、leucorrhea、white blood cell count、endometrial thickness、pregnancy rate.

3.2.6 Data management

All data will be double-input in the database by separated trained investigators and double-checked. SPSS or other statistical software will be used to analyze qualitative and quantitative indicators. All statistical tests were double-sided at the 0.05 level.

3.2.7 Postoperative management

Intravenous antibiotics will be used to prevent infection during the perioperative period (1 day total). Estrogen and progesterone will be administered from the day of surgery and estrogen is administered orally from the day of surgery for 21 days. Dydrogesterone tablets will be taken orally from the 12th day of operation for 10 days. The estrogen dose is 4–6 mg daily and the progesterone dose was 20 mg daily.

3.2.8 Statistical methods

All data will be statistically processed by SPSS 23.0 software. Measurement data will be expressed as mean ± standard deviation, and the three groups will be compared by ANOVA. LSD analysis will be used when variances are homogeneous, and Welch test will be used when variances are not homogeneous. If $P<0.05$, it is considered statistically significant and post hoc test multiple comparisons will be conducted. The *t*-test will be used to compare the two groups, and $P<0.05$ is considered statistically significant. Enumeration data is expressed by rate (%), and the Chi-square test or Fisher's precision probability test will be used for comparison. $P<0.05$ is considered statistically significant.

3.2.9 Informed consent and ethical issues

Approval from the ethics committee of Nantong Maternal and Child Health Hospital , Chinese academy of medical sciences will be obtained before the enrolment, and all participating hospitals should approve the study as well. Women will be adequately informed of the benefits and harms of participating in the study, completely voluntary, and they could drop out of the study at any time. Women could only participate in the study after signing the informed consent.

3.2.10 Quality control

①The researchers will strictly be included in the standards and exclusion criteria to select the research objects, and record the situation in detail and timely. After the second examination of hysteroscopy, the doctors of the Reproductive Pregnant Assistance Center will give timely and effective pregnancy guidance.

②The operation will be completed by doctors with secondary high school and above hysteroscopy certificate and many years of surgical experience.

③Data contents shall be input and input results by special personnel and kept by special personnel.

4. Innovation

This study has the following innovations:

4.1 In this study, the inclusion criteria of patients with moderate and severe adhesions will be strictly controlled according to the AFS score which can improve the accuracy

of the experimental results.

4.2 The three groups of patients will receive this hormone regimen simultaneously and at the same dose, facilitating the protective effect of estrogen in the prevention of adhesion.

4.3 In the present study, we recommend patients receive fertility guidance in the reproductive assisted pregnancy clinic of our hospital immediately after the second hysteroscopy, and their pregnancy status under different treatment methods will be followed up one year after surgery.

5. Trial registration

Trial registration: Chinese Clinical Trial Registry ChiCTR2100046945.

Article information: https://dx.doi.org/10.21037/apm-21-1296