Reproductive outcomes and reproductive tract microbiota shift in women with moderate-to-severe intrauterine adhesions following 30-day post-hysteroscopic placement of balloon stents or intrauterine contraceptive devices: A randomized controlled trial

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Summary

Background Intrauterine adhesions (IUA) develop in up to 20% of women with a history of abortion. After hysteroscopic adhesiolysis, balloon stents are usually placed for seven days to prevent recurrence. The efficacy of prolonged use (30 days) of balloon stents has not been determined.

Methods The trial was conducted from June 2019 to March 2021. Ninety-one patients who underwent hysteroscopic adhesiolysis for moderate or severe IUA were randomized to receive a 30-day placement of a balloon stent (n = 44) or an intrauterine device (IUD) (n = 47). The primary outcomes were the ongoing pregnancy and miscarriage rates assessed at 15-19 months. The secondary outcomes were the recurrence of IUA and the American Fertility Society (AFS) intrauterine adhesion scores at the first and second hysteroscopies, the diagnosis of new chronic endometritis at the second-look hysteroscopy, and the vaginal/uterine microbiome assessed using 16S rRNA sequencing. The trial was registered at Chinese Clinical Trial Registry (ChiCTR1900023306).

Findings The ongoing pregnancy rates (balloon 56·4% versus IUD 57·1%) and miscarriage rates (balloon 10·3% versus IUD 22·9%) were not significantly different between the groups. No differences in the recurrence of IUA, reduction of AFS scores, or new endometritis rates were detected. The bacterial load in the uterus and vagina increased in the IUD group but not in the balloon group.

Interpretation Balloon placement has a similar effect on ongoing pregnancy rates as intrauterine device (IUD) placement. Patients who underwent balloon placement had a lower miscarriage rate, although the difference was not significant. There were no differences in the recurrence rate of IUA, reduction of American Fertility Society scores, or rate of new chronic endometritis. The balloon stent has less effects on the uterine microbiota.

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Keywords: balloon; microbiota; intrauterine adhesions; intrauterine contraception device; hysteroscopic adhesiolysis

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Research in context

Evidence before this study

The optimal postoperative management for intrauterine adhesions (IUA) remains controversial. The clinical effectiveness of anti-adhesion treatments, such as inserted devices, hormonal treatment, and gel, are uncertain. However, barrier devices are used worldwide. Balloon stents are often placed inside the uterine cavity for seven days to prevent the recurrence of IUA after hysteroscopic adhesiolysis. However, the efficacy of prolonged placement (30 days) of balloon stents has not been fully demonstrated.

Added value of this study

Balloon placement has a similar effect on ongoing pregnancy rates as intrauterine device (IUD) placement. Patients who underwent balloon placement had a lower miscarriage rate (balloon 10·3% versus IUD 22·9%), although the difference was not significant. There were no differences in the recurrence rate of IUA, reduction of American Fertility Society scores, or rate of new chronic endometritis. The bacterial load in the uterus and vagina increased in patients with an IUD but not in those who underwent balloon placement.

Implications of all the available evidence

Balloon placement is as effective as IUD placement for the prevention of recurrent IUA following hysteroscopic adhesiolysis. Balloon placement has less effects on the uterine microbiota.

Introduction

The formation of intrauterine adhesions (IUA) in the uterine cavity and/or the cervical canal, also known as Asherman syndrome, occurs in 1·5% to 21·5% of female patients.[1] The prevalence of IUA after a spontaneous abortion is 19·1%.[2] IUA are thought to develop following the destruction of the basal layer of the endometrium as a result of spontaneous abortion,[2,3] pregnancy termination,[4] or retained products of conception.[5] During the healing process, the opposing walls of the uterus adhere together and cause minimal, marginal, or complete obliteration of the uterine cavity and cervical canal. Women with this disease suffer from menstrual abnormalities, infertility, recurrent pregnancy loss, and severe obstetric complications.[6]

Hysteroscopic adhesiolysis is the standard treatment for IUA, though it has a high rate of IUA recurrence.[6] According to a report from Cochrane database, the efficacy of anti-adhesion treatment to improve reproductive outcomes and decrease the recurrence of IUA after operative hysteroscopy is unknown.[7] Despite the inconsistencies in literature, some physicians usually administer post-operative cyclical hormone therapy or intrauterine devices including intrauterine contraception devices (IUD), foley catheters, and intrauterine balloons to prevent the recurrence of IUA.[8] Endometrial repair requires 1-2 menstrual cycles following hysteroscopic adhesiolysis. However, intrauterine balloons are typically used for only seven days due to theoretically increased risk of endometritis. A previous randomized trial reported no increase in bacterial colonization after an intrauterine balloon was placed for 30 days.[9] However, the previous study did not assess the recurrence rate or the long-term reproductive outcomes.

In this randomized controlled trial, the reproductive outcomes of balloon stent and IUD placement for 30 days were compared. It was hypothesized that the ongoing pregnancy rates at 15 months postoperatively would be higher among patients who underwent balloon placement compared to those who underwent IUD placement and that balloon placement decreases the rate of recurrence of IUA, decreases the adhesion score, and does not increase the risk of chronic endometritis or alter the endometrial microbiota compared to IUD placement.

Materials and methods

This prospective, randomized controlled, clinical trial was conducted from June 2019 to March 2021 at the Women's Hospital, Zhejiang University School of Medicine. The study was approved by the hospital's institutional review board (ECIRB 20190022) and was registered with the Chinese Clinical Trial Registry (ChiCTR1900023306). The study was conducted in accordance with the principles of the Declaration of Helsinki and all patients provided informed consent.

Patients

Women with menstrual problems or IUA-related endometrial ultrasound features were considered as possible IUA candidates. Patients aged 18-40 years with moderate to severe IUA based on the American Fertility Society (AFS) intrauterine scores[10] (AFS score $\geq$ 5) were included in this study. All patients agreed to undergo hysteroscopic adhesiolysis and endometrial biopsy and expressed a desire to have children in the future. Patients who were treated for acute bacterial infection within the month prior to the study; those with a history of lower genital tract medication or irrigation within the month prior to the study; those with a history of reproductive tract surgery within three months prior to the study; those with infertility due to male factors, fallopian tube factors, or anovulation; those with contraindications for estrogen or progestin use; or those diagnosed with reproductive system tumors, coagulation disorders, tuberculosis, diabetes, or uterine malformation were excluded from the study.

Randomization was conducted using computer generated numbers sealed in envelopes at a 1:1 ratio by the research coordinator. The gynecologists opened the envelopes after finishing the major steps of the first-look hysteroscopy and allocated the patients accordingly. Patients underwent a balloon or an IUD placement immediately after the hysteroscopy.

Follow-up for pregnancy and miscarriage was conducted by interviewing the participants by phone at 15-19 months after the second-look hysteroscopy.

Blinding

The clinicians who were not involved in the balloon or IUD placement, those who performed data analysis, family members of the patients, and all study personnel remained blinded to the group assigned. However, it was not possible to blind the gynecologists who placed the devices or the patients. The participants were not blinded because the balloon and IUD can be differentiated by feeling during placement.

Hysteroscopic procedures and sample collection

All the patients underwent hysteroscopic surgery twice and were asked to abstain from sexual intercourse between the two operations. The first-look hysteroscopy was performed during the follicular phase of the menstrual cycle (day 5-12). To prime the cervix, 40 mg of phloroglucinol was administered intravenously 30 minutes prior to surgery. We chose phloroglucinol over misoprostol because phloroglucinol causes lesser pain and dilates the cervix better.[11] A 30° forward-oblique hysteroscopy was introduced, and the resection of adhesions was performed with a monopolar electrode (Wolf, Germany) after prudent dilatation of the cervix using Hegar dilators. Distension of the uterine cavity was achieved using 5% glycine. According to the patient's allocation, a heart-shape balloon stent (Obgyn, Jiangsu, China) or a uterine-shaped copper IUD (Yantai Contraceptive Instrument Company, Shandong, China) was inserted into the uterine cavity at the end of the procedure (Figure 1). The device's position was adjusted using the hysteroscope, and the balloon's tail extending from the cervix was cut. No antiadhesive gel was used postoperatively.

Estrogen/progesterone therapy was administered between the hysteroscopic procedures. The patients were administered 6 mg/d estradiol valerate for 21 days and 20 mg/d dydrogesterone for 10 days (starting on day 12 of estrogen therapy). On day 3 of the next menstrual cycle, hormone therapy was restarted with 6 mg/d estradiol valerate tablets.

The second-look hysteroscopy was performed on days 7-10 of the subsequent menstrual cycle. A 30° forward-oblique hysteroscopy (Karl Storz, Germany) was used after cervical priming. Physiological saline was utilized to distend the uterine cavity. Recurrent adhesions were identified and adhesiolysis of newly formed IUA was conducted with miniature scissors. After completing the hysteroscopy, the balloon or IUD was removed. Two additional cycles of estrogen/progesterone therapy were administrated after the second-look hysteroscopy.

To collect samples for the assessment of the microbiota, the perineum was disinfected and draped, then an applicator swab (Copan Venturi Transystem, Copan, Italy) was used to swab the posterior vaginal fornix. Next, the vagina and cervical canal were disinfected with 5% povidone-iodine, and samples of the endometrial layer and flora were obtained using an endometrial biopsy device with an outer shell and internal penniform plastic core (Saipujiuzhou Sci-Tech, Beijing, China) prior to the injection of 5% glycine for the hysteroscope.

Outcomes

The primary study outcomes were the ongoing pregnancy and miscarriage rates at 15-19 months after the second-look hysteroscopy. Ongoing pregnancy was defined as the occurrence of any pregnancy over 12 weeks of gestation during the follow-up period. Miscarriage was defined as any pregnancy loss before 12 weeks of gestion during the follow-up period.

The secondary outcomes were the recurrence rate of IUA, AFS intrauterine adhesion scores at the first and second hysteroscopies, diagnosis of new chronic endometritis at the second-look hysteroscopy, and changes in the vaginal/uterine microbiome. New chronic endometritis was defined as chronic endometritis at the second-look hysteroscopy that was absent at the first-look hysteroscopy.

Diagnosis of IUA and chronic endometritis

The severity of IUA was determined according to the AFS classification system (1988 version).[10] Mild, moderate, and severe adhesions were defined as an AFS score of 1-4, 5-8, and 9-12, respectively. Recurrent IUA was defined as adhesions observed during a second-look hysteroscopy after a successful adhesiolysis during the first-look hysteroscopy. The diagnosis of chronic endometritis was determined by the presence of plasma cells identified by CD138 immunohistochemical staining.[12] Briefly, slides were incubated overnight with a 1:50 dilution of mouse monoclonal antibody clone B-A38 against human Syndecan-1 (Cell Marque, UK) at 4°C. The slides were then incubated with secondary rabbit anti-mouse horseradish peroxidase–labeled antibody ab97046 (Abcam, UK) for one hour. The cells were considered as CD138+ plasma cells if they exhibited complete, unambiguous, brown staining with intact cell membranes.

Microbiome sequencing

The microbiome sequencing and analysis were conducted as previously described.[13] Briefly, the microbial

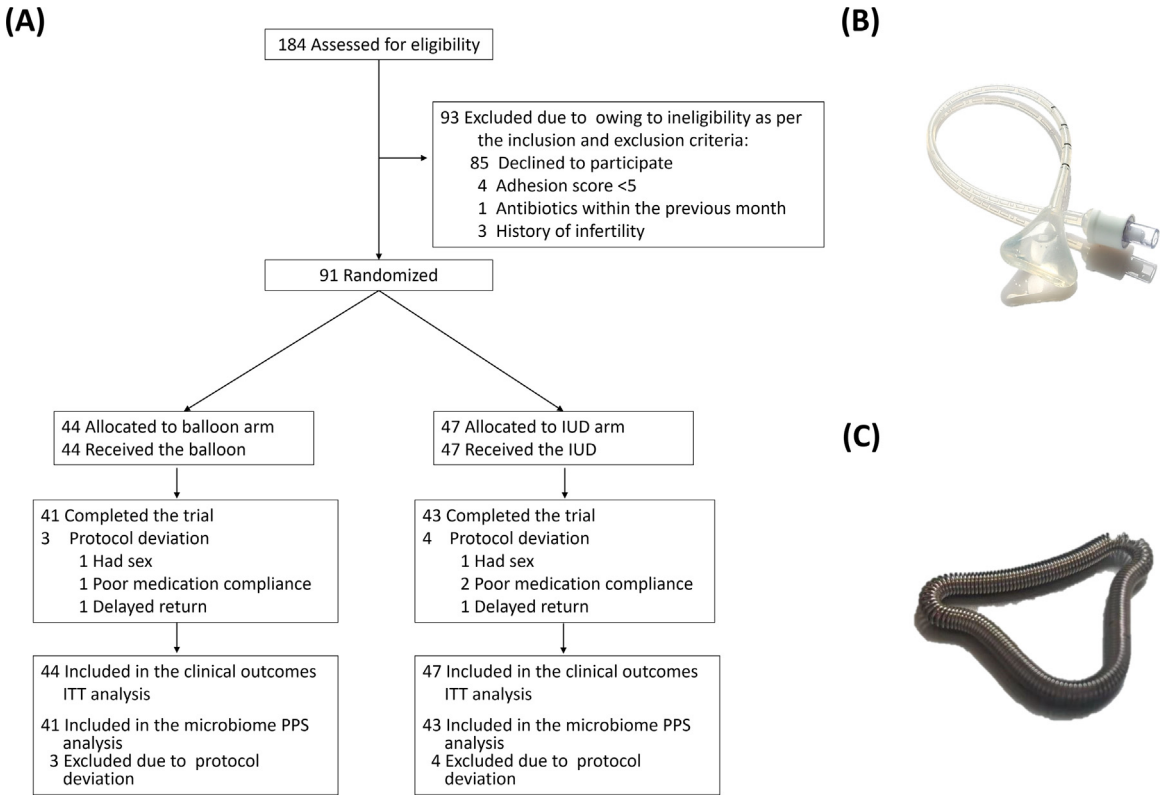

Figure 1. Study flow chart (A) and images of the balloon (B) and IUD (C). IUD, intrauterine device; ITT, intention to treat; PPS, per protocol set.

DNA extracted from the vaginal swab and endometrial biopsy samples was amplified using V3-V4 PCR primers (341F and 806R). The PCR amplicons were quantified using Qubit3·0 (Invitrogen, Thermo Fisher, US) and sequenced using Illumina MiSeq at Mingke Co., Ltd., in Zhejiang, China. The raw reads were deposited into the NCBI Sequence Read Archive (Accession Number: PRJNA699731). The reads were clustered into operational units with a 97% similarity cutoff using UPARSE v7·1. The phylogenetic affiliation of each 16S rRNA gene sequence was analyzed by RDP Classifier against the Silva (SSU115).[14] Principal coordinate analysis (PCoA) was performed using the ape library in the R program. The calculation of the alpha-diversity and the Adonis test were performed using vegan and picante R-packages. Shannon and ACE were used to measure the alpha-diversity, and higher indices indicated a higher extent of richness and evenness of the microbiota.

Statistical analyses

The ongoing pregnancy rate was assumed to be 60 % for the IUD group and 70% for the balloon group with a standard deviation of 15 for both group.[6,15,16] Therefore, 36 participants were required for each group to obtain an 80% power to detect the difference between the groups at a significance level of 0·05. The sample size was calculated using an online tool (https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html). Considering the drop-out, 100 randomized patients were recruited to yield 72 participants to complete the trial. The study was terminated when the prespecified number of patients was recruited, and no interim analyses were conducted.

The statistical analyses were conducted primarily using an intention-to-treat (ITT) basis for the clinical outcomes and an in per protocol set for the microbiome analysis. The clinical outcomes were analyzed using SPSS version 19·0 (IBM, Chicago, IL, USA). Continuous variables were analyzed using a Student t-test or a Mann-Whitney U test, and categorical variables were analyzed using a chi-squared test. Relative risks and 95% confidence intervals were generated for the reproductive outcomes. The statistical significance was set at $p < 0·05$ or a 95% confidence interval crosses one.

Role of funding

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approval of the manuscript; or the decision to submit the manuscript for publication.

Results

Of the 184 patients assessed for eligibility, 93 were excluded (85 declined to participate, four had AFS scores < 5, three had a history of infertility, and one had a history of antibiotic use within the month prior to the study). Forty-four patients were assigned to the balloon group, and 47 were assigned to the IUD group (Figure 1). All the patients received treatment per protocol. Seven women deviated from the protocol (three had poor medication compliance, two had sex, and two had delayed returns). These seven patients were still included in the final analysis set for the clinical and reproductive outcomes due to the intention to treat inclusion principle. The patients' age, BMI, gravidity and parity, and contraception methods were not significantly different between the groups (Table 1, p = 0·58, 0·49, 0·62, 0·86 and 0·26, respectively).

Recurrence and AFS intrauterine adhesion scores

Adhesiolysis was performed for each patient during the first-look hysteroscopy. The recurrence rates were not significantly different between the groups (balloon group = 50·0%; IUD group = 55·3%, p = 0·61) (Table 2). The AFS scores at the second-look hysteroscopies were significantly lower than those at the first hysteroscopies for both groups; however, score reductions were not significantly different between the two groups (balloon 6·3 versus IUD 5·6, p = 0·22) (Table 2).

Chronic endometritis

Five new cases of chronic endometritis were identified during the second-look hysteroscopies in the balloon group and 11 were identified in the IUD group, though the difference was not significant (p value = 0·11) (Table 2).

Reproductive outcomes

Thirty-nine patients in the balloon group and 35 in the IUD group attempted to conceive following the second-look hysteroscopies. Of these women, 22 (56·4%) in the balloon group and 20 (57·1%) in the IUD group had an ongoing pregnancy. All the pregnancies occurred spontaneously without the help of assisted reproductive technologies. The rates of ongoing pregnancy were not significantly different between the groups (risk ratio (RR): 0·98; 95% confidence interval (CI): 0·66 - 1·47). Four patients (10·3%) in the balloon group and eight (22·9%) in the IUD group had miscarriage. The miscarriage rate was not significantly different between the two groups (RR: 0·45; 95% CI: 0·66 - 1·36) (Table 3). A sensitivity analysis using per-protocol analysis is provided (Supplementary table). The conclusion is unchanged.

Uterine and vaginal microbiota

The bacterial load was not significantly different in the uterine (p = 0·25) or vaginal microbiota (p = 0·49) at the first- and second-look hysteroscopies in the balloon group (Figures 2A and 2B). In contrast, the uterine (p <

Variable	Balloon (n=44)	IUD (n=47)	P-value
Age (years)	30·5±5·1	30·0±4·20	0·58
BMI (kg/m^2)	21·1±2·7	21·5±2·6	0·49
Gravidity			0·62
1	10 (22·7%)	14 (29·8%)	
2	16 (36·4%)	18 (38·3%)	
≥3	18 (40·9%)	15 (31·9%)	
Parity			0·86
0	25 (56·8%)	26 (55·3%)	
1	18 (40·9%)	19 (40·4%)	
2	1 (2·2%)	2 (4·3%)	
Previous contraception			0·26
No birth control	15 (34·1%)	11 (23·4%)	
Condom	29 (65·9%)	36 (73·6%)	
Menstrual pattern			0·45
Normal	5 (11·4%)	8 (17·0%)	
Hypomenorrhea	39 (88·6%)	38(80·9%)	
Amenorrhea	0 (0%)	1 (2·1%)	
Peri-ovulatory endometrium thickness (mm)	5·7±2·2	6·4±2·0	0·13

***Table 1*: A comparison of the baseline characteristics in the two groups.**
Data were mean± standard deviation or number (percentage%). Variables were compared using Student t-test or Mann-Whitney U test, as appropriate.
IUD, intrauterine device.

	Balloon (n=44)	IUD (n=47)	P-value
Adhesion classification at first-look hysteroscopy			0·23
Moderate	33 (75·0%)	40 (85·1%)	
Severe	11 (25·0%)	7 (14·9%)	
Mean AFS scores at first-look hysteroscopy	8·0 ±1·4	7·7±1·4	0·28
Adhesion classification at second-look hysteroscopy			0·76
No adhesion	22 (50·0%)	21 (44·7%)	
Moderate	16 (36·4%)	17 (36·2%)	
Severe	6 (13·6%)	9 (19·1%)	
Mean AFS scores at second-look hysteroscopy	1·8±2·0	2·0±2·0	0·53
Reductions in AFS scores from first-look to second-look hysteroscopy	6·3±2·5	5·6±2·1	0·22
Recurrence rate at second-look hysteroscopy	22 (50·0%)	26 (55·3%)	0·61
New chronic endometritis at second-look hysteroscopy (%)	5 (12·2%)	11 (25·5%)	0·11

***Table 2*: The recurrence, AFS intrauterine adhesion scores and new endometritis at the two consecutive hysteroscopies.**
Data were mean± standard deviation or number (percentage). Variables were compared using Student t-test.
AFS, American Fertility Society. IUD, intrauterine device.

	Balloon (n=39)	IUD (n=35)	RR (95% CI)*
	n (%)		
Ongoing pregnancy	22 (56·4%)	20 (57·1%)	0·98 (0·66 -1·47)
Miscarriage	4 (10·3%)	8 (22·9%)	0·45 (0·66 - 1·36)

***Table 3*: Reproductive outcomes following treatment with balloon or IUD.**
RR, relative risk.
* , IUD as the reference group.IUD, intrauterine device.

0·001) and vaginal (p = 0·008) bacterial loads increased after the first-look hysteroscopy in the IUD group.

The bacterial composition was found to be more monotonous after the first-look hysteroscopies (Figure 2C). *Prevotellaceae, Lactobacillaceae* and *Lachnospiraceae* bacteria were more abundant, and the abundance of *Planctomycetaceae* decreased (Supplementary Figure S1). These findings were supported by the PCoA analysis. While the uterine microbiota samples collected from the two consecutive hysteroscopies were distinct from each other in both groups, the vaginal microbiota did not change significantly between the two consecutive hysteroscopies in terms of the alpha- or beta-diversity in each group. In addition, no significant differences were found in the alpha- or beta-diversity for the uterine and vaginal microbiota during the two hysteroscopies between the two groups (Figures 2C, 2D, and Supplementary Figure S2).

Discussion

The results of this study indicate that balloon stents and IUDs have similar efficacy in terms of ongoing pregnancy and miscarriage rates at 15 - 19 months post-hysteroscope and similar recurrence rates and AFS scores during the second-look hysteroscope in patients with a history of IUA. However, the balloon stent affects the microbiota less, and therefore may be preferable to the IUD. To our knowledge, this is the first study to evaluate the recurrence rate of IUA and the reproductive outcomes following 30 days of balloon placement post-operation.

The optimal postoperative management for IUA is controversial. Several meta-analyses[17–19] have assessed the various post-hysteroscopic anti-adhesion treatments. The clinical effectiveness of anti-adhesion treatments, including inserted devices, hormonal treatment, and gel, remain uncertain.[18,19] One meta-analysis from the Cochrane database, reported no difference in live birth rates between patients who underwent treatment and those who received no treatment or placebo, although anti-adhesion therapy was associated with a lower recurrence rate at the second-look hysteroscopy. Although no proven treatment is available, hormonal treatment, gel, and barrier devices are widely used worldwide. At our institution, three months of hormonal treatment and barrier devices inserted post-hysteroscopically are the standard of care.

Copper IUDs were used as a control device in this study just as in previous studies.[20–22] IUA occur more frequently in developing countries where abortion is common and the copper IUD is more affordable to patients in these regions. The shape of the copper IUD fits the uterine cavity well, preventing the recurrence of lateral and cornual IUA. However, the release of Cu^{+} from the IUD may lead to endometrial bleeding and chronic endometritis and can be toxic to sperm and embryos.[23] Therefore, it was not unexpected that the IUD group in this study had a higher miscarriage trend although not significant. However, the use of copper IUDs in patients with IUA is paradoxical, as most of these patients desire to conceive. The Cu^{+} released from the IUD may also be associated with the increased bacterial load observed in the IUD group, as recent studies

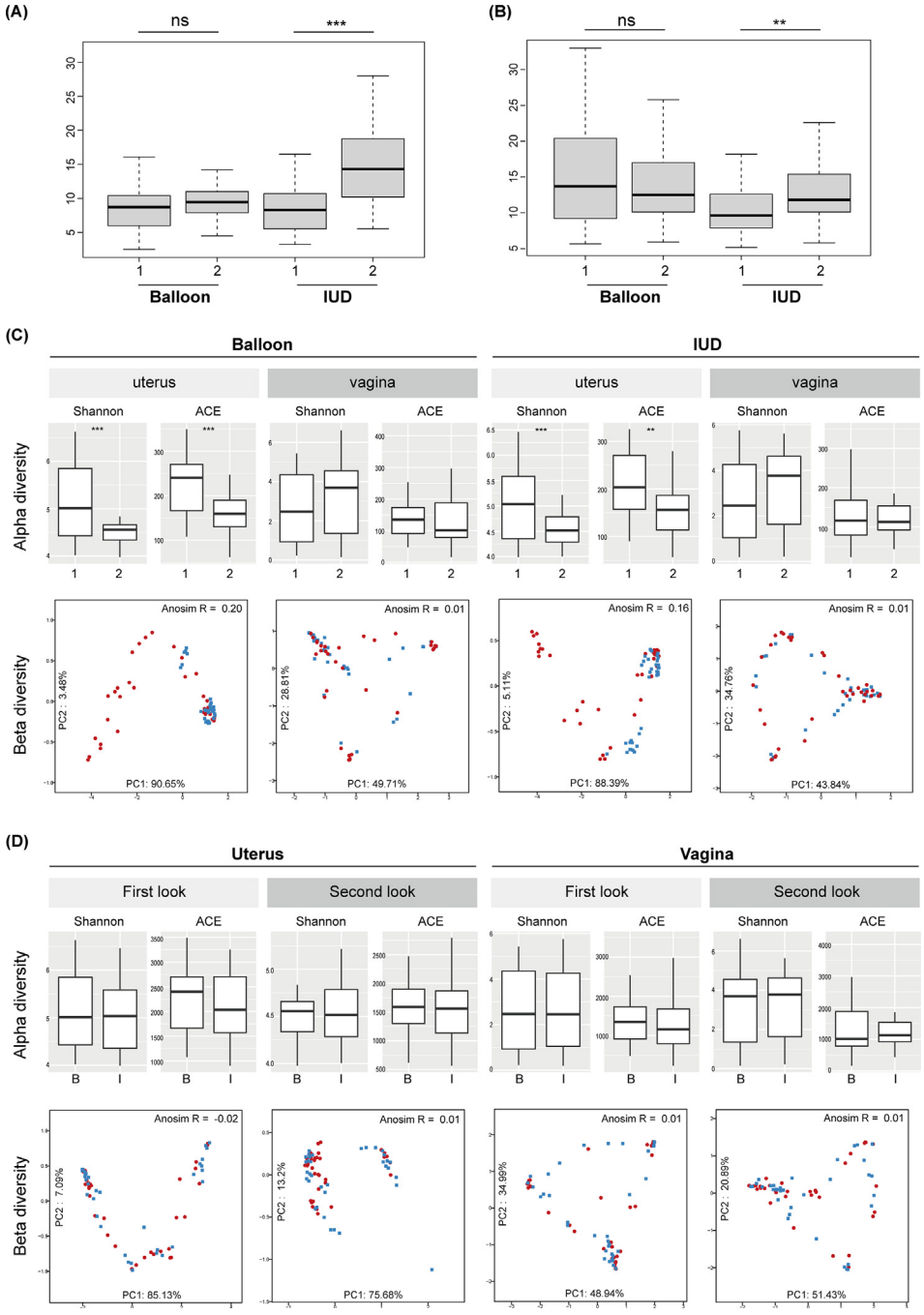

Figure 2. Impact of balloon and IUD on the uterine and vaginal microbiota.

Panel A and B shows the quantitative comparisons of the bacterial DNA between the first-look and second-look hysteroscopic surgeries for uterine microbiota and for vaginal microbiota, respectively. The Y-axis represents the DNA quantity (ng) per ul of the 16s rRNA PCR amplicon. Panel C and D shows the comparisons of the uterine and vaginal microbiota between the first- and second-look hysteroscopic surgeries, and between the balloon and IUD groups, respectively. Analysis of alpha-diversity includes Shannon and ACE indices. Analysis of beta-diversity was performed by PCoA. In panel C, red dots on the PCoA plots represent samples collected at the first-look hysteroscopy, whereas blue dots represent those collected at the second-look hysteroscopy. In panel D, red dots represent samples from the balloon group, and blue dots represent those from the IUD group. For the box plots, the central lines within the box indicate the median, the boxes indicat the 1st and 3rd quartiles, and the whiskers indicate the minimum and maximum. The numbers 1 and 2 represent the first- and second-look hysteroscopies. The symbols B and I represent the balloon and IUD groups. NS, not significant; ***, $p<0.001$, **, $p<0.01$.

have suggested that IUDs are associated with bacterial vaginosis and *Actinomyces* species infections,[24–26] and that the risk of infection is proportional to the length of the IUD placement.[24,27,28]

All patients in this study were found to have moderate to severe IUA at the time of the first-look hysteroscopy. The AFS scores decreased significantly between the two hysteroscopies in both groups, which is consistent with the findings of previous studies.[20,21] However, mild recurrent adhesions were observed during the second-look hysteroscopy. Previous studies have reported pregnancy success rates of 80% for women with mild IUA, 65% for women with moderate IUA, and 30% for women with severe IUA, which are consistent with the rates observed in both groups in this study.[6,15,16] As the AFS scores during the second-look hysteroscopies were low (mostly < 5) and the overall pregnancy rate was satisfactory, a second-look hysteroscopy may not be necessary in these patients. A simple procedure to remove the balloon or IUD and any newly-formed IUA may be sufficient.

Previous studies have reported that the uterine cavity is not sterile.[29,30] The presence of bacteria in the uterus may indicate colonization, and does not necessarily indicate infection.[31] The source of these bacteria and their effect on women's health remains unknown. The use of the balloon and IUD increased the amount of the common vaginal flora, *Prevotellaceae, Lactobacillaceae,* and *Lachnospiraceae* in this study. Therefore, following the insertion of intrauterine stents, the composition and permeability of the cervical mucus plugs may change, allowing the vaginal bacteria to migrate to the uterus more easily.

This study is the most comprehensive evaluation regarding the fertility and microbiota outcomes of IUA treatments using balloon stents and IUDs to date. Previous studies have suggested that balloon placements for 3-7 days,[32] 7 days[20] and 14 days[33] are safe, though these studies were based on clinical manifestations. One previous study identified the microbes within the uterus 30 days after balloon placement; however, the microbes were tested using a traditional culture approach,[9] which is less sensitive than 16s rRNA sequencing.[34] In this study, the 16s rRNA sequencing method was used to determine the bacterial profile of the vaginal and uterine microbiota in a direct and comprehensive manner, allowing for a better evaluation of the microbial safety of the balloon stent and IUDs.

This study is not without limitations. First, the follow-up period may not be sufficient. Because of the limited follow-up period, we cannot provide delivery information (e.g. live birth rate or preterm delivery rate). However, due to limited funding, the follow-up period could not be extended. Second, this study did not include a traditional control group as there is no standard treatment for post-hysteroscopic IUA recurrence. Copper-IUD placement was used as a control because it is a well-accepted treatment. However, we cannot rule out the effects of copper on reproduction. Third, this study is underpowered to detect the difference in miscarriage rate due to the relatively small sample size. Thus, we recommend future studies with larger sample size taking the non-copper IUD as the control group to improve the quality of the study.

In conclusion, the use of balloon stents and IUDs result in similar long-term reproductive outcomes in women with IUA. Though both devices have similar efficacy against recurrent IUA, balloon stents affect the uterine microbiota less than IUDs.

Author Contributions

Dr. Gufeng Xu and Dr. Yue Wang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Yue Wang, Yu Zhao, and Gufeng Xu

Acquisition, analysis, or interpretation of data: Yuan Ge, Jin Cen, and Gufeng Xu

Drafting of the manuscript: Yue Wang and Yu Zhao

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Gufeng Xu

Obtained funding: Yun Liao

Supervision: Yue Wang and Gufeng Xu

Data Sharing Statement

The data and protocol are available upon request by contacting the corresponding author.

Declaration of Competing Interest

The authors report no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101200.

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