Reproductive outcomes following copper-containing intrauterine device after hysteroscopic lysis for intrauterine adhesions

PAN XU[1,2*], HENG XU[1,2*], QIAOQIAO LU[1], SHANSHAN LING[1], E HU[1], YING SONG[1], JIE LIU[1] and BIXIA YI[1]

[1]Department of Gynecology, Affiliated Jinhua Hospital of Wenzhou Medical University, Jinhua, Zhejiang 321000; [2]Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310006, P.R. China

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Abstract. The present study aimed to investigate the reproductive outcomes of copper-containing intrauterine devices (IUDs) after hysteroscopic lysis in patients with mild to severe intrauterine adhesions (IUAs), according to the American Fertility Society (AFS) classification. Therefore, a prospective randomized controlled study was conducted at the Affiliated Jinhua Hospital of Wenzhou Medical University (Jinhua, China). A total of 173 women with IUAs were initially recruited between January 2020 and June 2021 and were then randomized to the copper-containing IUD group or the no barrier device group. Following hysteroscopic procedure, the fertility and obstetric outcomes were analyzed. Among the 173 patients enrolled, a total of 109 participants completed the study protocol. The results showed that AFS scores were not significantly different between the two groups prior to hysteroscopy. In addition, no statistically significant differences were recorded in pregnancy and live birth rates between the copper-containing IUD and no barrier device groups. Overall, the results of the current study indicated that the copper-containing IUDs had no positive effect on pregnancy and live birth rates in patients with mild to severe IUAs after hysteroscopic adhesiolysis. The present trial was retrospectively registered in the Chinese Clinical Trial Registry on 28th December 2023 (registration no. ChiCTR2300079233).

Introduction

Intrauterine adhesions (IUAs), also known as Asherman syndrome, is a common gynecological disease in clinical practice that is accompanied by several symptoms, such as pain, menstrual disturbance and subfertility (1). The majority of IUA cases are associated with trauma to the endometrial basalis layer caused by curettage, hysteroscopy, intrauterine infections and genital tuberculosis (2). The incidence and prevalence of IUAs vary in different studies. A review article by Yu *et al* (3) reported that the incidence of IUAs in 2,981 patients was 770/2,981 in Israel, 456/2,981 in Greece and 445/2,981 in South America. Another study indicated that the incidence of IUAs was 16-19%, as verified by hysteroscopy after miscarriage curettage. Additionally, this study also reported that the risk of IUAs was notably increased by 40% after repeated curettage (4).

It is widely accepted that hysteroscopy is the most accurate method for the diagnosis and treatment of IUAs. It has been also reported that hysteroscopic lysis performed using hysteroscopic scissors without electrosurgery provides protection to the endometrium (5-7). Due to the high rate of adhesion reformation (21.0-41.9%) (8), the prevention of IUA recurrence following operation is crucial for the therapeutic outcome. Several types of precautions can be taken to achieve this purpose, including the application of crosslinked hyaluronic acid gels, balloon catheters, intrauterine devices (IUDs), estrogen, aspirin and stem cell treatment (1,8-10). The insertion of an IUD to separate the endometrial layers after the hysteroscopic lysis of IUAs has been applied for several years. However, due to their inflammatory-promoting properties, copper-containing IUDs are not recommended. However, when non-copper IUDs were removed from the market (3), the use of copper-containing IUDs after hysteroscopy is likely to increase in clinical practice. Nevertheless, the data regarding subsequent fertility and obstetric outcomes after the use of copper-containing IUDs following hysteroscopy are limited. Therefore, the present prospective, randomized controlled trial (RCT) was carried out to investigate the efficacy of copper-containing IUDs on reproductive outcomes after hysteroscopic adhesiolysis in women treated for IUAs.

Subjects and methods

Subjects. This present study was approved by the Medical Ethics Committee of the Affiliated Jinhua Hospital of Wenzhou Medical University (approval no. IRB-2020028-R; Jinhua, China) and was conducted at the same hospital

Correspondence to: Dr Bixia Yi, Department of Gynecology, Affiliated Jinhua Hospital of Wenzhou Medical University, 267 Danxi East Street, Jinhua, Zhejiang 321000, P.R. China
E-mail: panxu527@163.com

*Contributed equally

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between January 2020 and June 2021. The inclusion criteria were as follows: i) Patients who met the diagnostic criteria for IUAs by hysteroscopy; ii) patients who were willing to participate in the study and signed the informed consent form; iii) female patients aged 23-50 years (11-13); iv) patients who suffered from mild to severe IUAs, according to the American Fertility Society (AFS) classification system (3); and v) patients who wished to become pregnant. The exclusion criteria were the following: i) Patients who had contraindications for estrogen-progesterone therapy and hysteroscopy, including severe coagulation disorders, severe heart, liver and kidney diseases or mental disorders; ii) patients who suffered from female genital tuberculosis, endometrial polyps, submucous myoma and endometrial carcinoma; and iii) women with postmenopausal status.

Sample size calculation. In the present research, it was hypothesized that the live birth rates were 50% in patients with IUDs and 20% in patients without any barrier device, as indicated in previous literature (1-3). By accepting a type I error (α) of 0.05 and a type II error (β) of 0.1, the number of patients with IUAs required for each group was 54. Estimating a drop-out rate of 30%, a total of 140 subjects were required.

Patient grouping. Patients who fulfilled the inclusion criteria and signed informed consent to participate in the study were randomized into the treatment or control groups using a computer randomization method. After completing the procedure of hysteroscopic adhesiolysis during the follicular period, patients in the treatment group used copper-containing IUDs, while those in the control group did not use any barrier device. The hysteroscopic adhesiolysis procedure was repeated (2-3 times) until the uterine cavity was recovered, as verified by two experienced gynecologists (PX and BY).

Treatment. Patients without history of allergies received antibiotic prophylaxis with intravenous injection of 1.5 g cefuroxime 30 min prior to surgery. Once IUA was assessed and verified, patients underwent hysteroscopy with a 5.0 mm outer diameter hysteroscopy (Richard Wolf GmbH) to divide the adhesions using hysteroscopic scissors without electrosurgery under local anesthesia. The intrauterine pressure was maintained at 120 mmHg and normal saline was used as a distension medium. Transabdominal ultrasonography was applied throughout the operation. Each patient was orally administrated with 4 mg/day estradiol (dydrogesterone tablets) for the first 14 days and 20 mg/day complex packing estradiol tablets/estradiol and dydrogesterone tablets (2 mg/2 mg and 10 mg; Abbott Biologicals B.V.) for the last 7 days after hysteroscopy. During the interval between operations (4 weeks), all patients also received low-dose aspirin (75 mg/day). The IUDs remained in the uterine cavity for 4 weeks. The second look hysteroscopic therapy was carried out ~4 weeks after the first surgery. In addition, if a patient suffered from severe adhesion recurrence, the third hysteroscopic procedure was usually performed at ~4 weeks after the second surgery. After the completion of the aforementioned treatment, the patient underwent natural conception or assisted reproduction, followed up bimonthly for 1.5 years, and the fertility outcome was recorded. The data of the present study were collected and managed by the electronic medical record system of the Affiliated Jinhua Hospital of Wenzhou Medical University.

Pregnancy definition. Pregnancy was verified by detecting fetal cardiac activity using transvaginal ultrasound. Live birth was defined as ≥28 completed weeks of live birth gestation, while preterm birth was defined as ≥28 completed weeks, but prior 37 completed weeks of live birth gestation. Placenta accreta spectrum or adherent placenta disorders were diagnosed using ultrasound, nuclear magnetic resonance imaging or during surgery.

Statistical analysis. All statistical analyses were performed using SPSS version 25 software (IBM Corp.). The continuous variables of the clinical characteristics are presented as the mean ± SD or the median (P25, P75). The differences between the groups were compared using independent-sample Student's t-test or Wilcoxon rank-sum test. Dichotomous variables are presented as n (%) and were analyzed using χ^2 test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. The flow chart of subject recruitment, randomization and follow-up is shown in Fig. 1. Of the 173 women that were originally recruited, a total of 17 patients were excluded and the remaining 156 were randomly allocated into the treatment (n=77) and control (n=79) groups. Finally, 109 patients completed the study and final analysis. After the first operation, a total of 33 patients changed the treatment plan and did not try to conceive during the follow-up period, which included 25 patients in the treatment group and 8 patients in the control group. A total of 11 patients were lost to follow-up, 4 patients in the treatment group and 7 patients in the control group. A total of 3 patients were reluctant to continue the study, 2 patients in the treatment group and 1 patient in the control group. The basic characteristics, including age, body mass index, parity, miscarriage times and AFS scores were compared between the two groups. As shown in Table I there were no statistically significant differences between the two groups. By contrast, hysteroscopy frequency was significantly higher in the treatment group compared with the control group.

Pregnancy and live birth rates after hysteroscopy. As previously stated, a total of 109 patients were eligible and tried to get pregnant. Among them, 38/46 (82.6%) patients in the treatment group and 55/63 (87.3%) in the control group underwent *in vitro* fertilization and embryo transfer using artificial reproductive techniques. No statistically significant difference was observed between the two groups (Table II). The comparison of pregnancy rates between the two groups after hysteroscopy are shown in Table III. The pregnancy rate in the treatment group (60.9%) was lower compared with that in the control group (66.7%). However, statistical significance was not reached ($P>0.05$). Furthermore, the live birth rate after hysteroscopy in the treatment group (41.3%) was lower compared with that in the control group (55.6%). However, again, no statistically significant differences were obtained between the two groups ($P>0.05$; Table III).

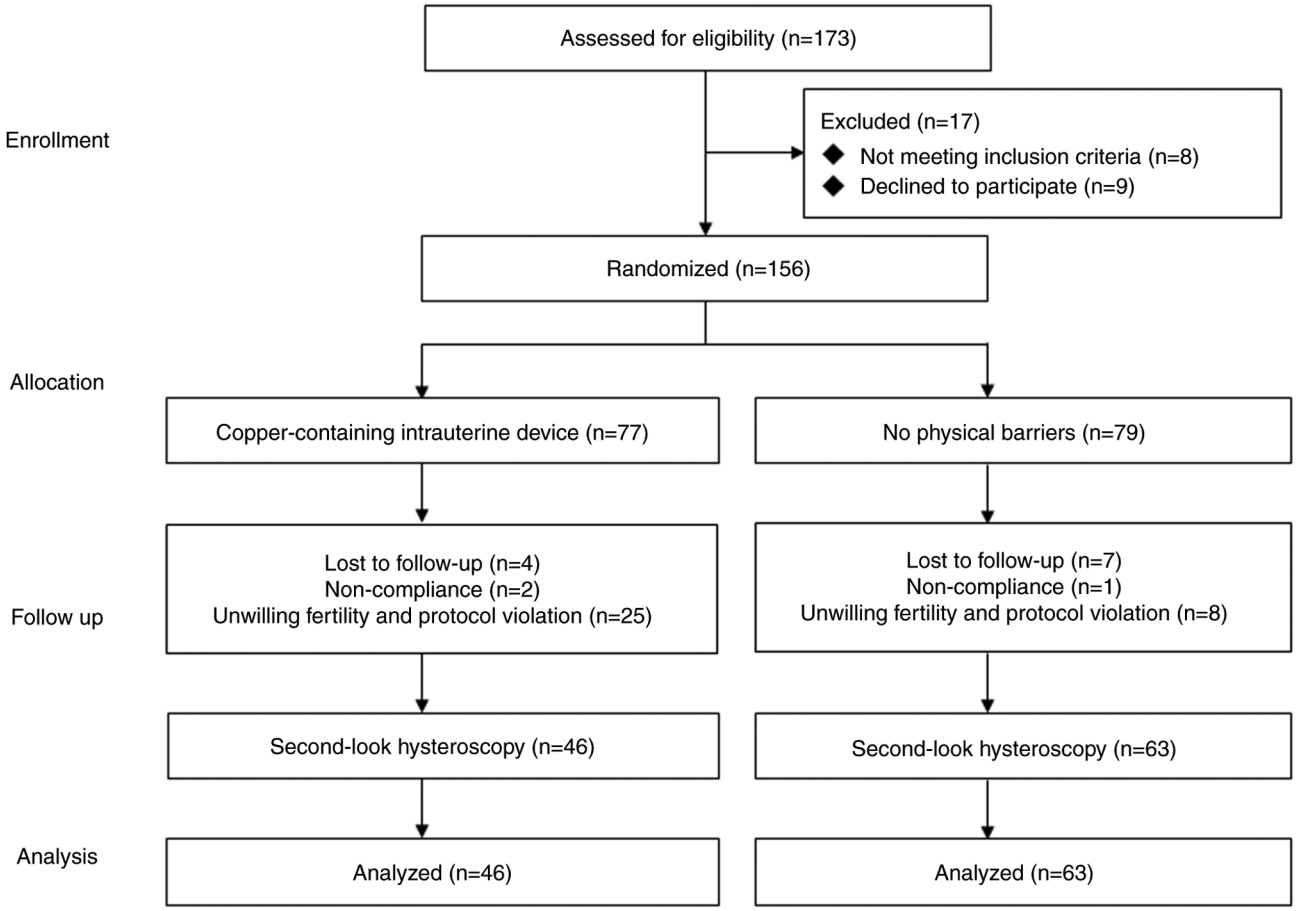

Figure 1. Flow chart of subject recruitment, randomization and follow-up.

Obstetric outcomes after hysteroscopy. The obstetric outcomes between the two groups were compared as shown in Table IV. Among all patients included in the present study, 54/109 (49.54%) had at least one live birth, while 8/54 gave twin live birth. In addition, 36/54 (66.67%) women underwent cesarean delivery, 10/54 (18.82%) had adherent placenta and placenta accreta, while 3/54 (5.56%) received blood transfusion. Additionally, 2/54 patients (3.70%) underwent abdominal hysterectomy and 5/54 (9.26%) gave premature birth. No neonatal deaths were recorded.

Discussion

Hysteroscopic lysis of adhesions is an effective and standard approach for the diagnosis and treatment of IUAs. Due to the high rate of adhesion reformation after primary hysteroscopy, preventing the recurrence of IUAs after operation is of important for their cure. IUDs and other mechanical barriers have been widely used to separate the endometrial layers for endometrial regeneration. The use of IUDs has been considered as a standard approach for maintaining uterine cavity (7). Due to the induction of inflammatory responses, the application of copper-containing IUDs is not recommended. However, the use of copper-containing IUDs after hysteroscopy is likely to increase in clinical practice when non-copper IUDs are withdrawn from the market. There are limited data regarding subsequent fertility and obstetric outcomes in patients using copper-containing IUDs (1). Therefore, a prospective RCT was conducted in the present study to investigate the reproductive outcomes of patients using copper-containing IUDs. A major limitation of the present study was that a control arm, involving patients treated with IUDs without copper, was not included.

In the current study, the reproductive outcomes in patients treated for IUAs between the copper-containing IUD (treatment group) and the no-barrier device (control group) groups following hysteroscopic lysis were compared. The live birth rate is considered to be the most significant clinical outcome in women with IUAs who wish to become pregnant (3). In the present study, a 60.9 and 66.7% pregnancy rate was recorded in the treatment and control group, respectively. The pregnancy rates in both the treatment and control groups in the present study were higher than those reported by Pabuccu *et al* (11) (30 and 47.2%, respectively) and similar to those recorded in the study by Huang *et al* (12) (58.9%) in 2020. However, no significant differences were observed in both pregnancy and live birth rates between the two groups. With a live birth rate of 41.3% in the treatment group and 55.6% in the control group, a total of 49.54% of patients gave at least one live birth. The aforementioned results were consistent with those reported by Huang *et al* (12). In the prospective RTC by Huang *et al* (12), 171 patients were randomly allocated into the balloon insertion and contraceptive IUDs plus Foley catheter groups. No statistically significant differences were recorded in the pregnancy and live birth rates between the two groups (12).

Table I. Comparison of the clinical characteristics of patients between the treatment and control groups after hysteroscopy.

Characteristic	Treatment group (n=46)	Control group (n=63)	P-value	t/z value
Age, years[a,b]	33.88±0.71	33.36±0.69	0.605	0.519
BMI, kg/m^2[a,b]	22.32±0.45	23.18±0.44	0.178	1.358
Parity[c,d]	0 (0,1)	0 (0,1)	0.486	0.696
Miscarriages[c,d]	1 (1,2)	2 (1,2)	0.860	0.177
AFS score[a,d]	6.20±0.23	5.74±0.14	0.094	1.694
Hysteroscopy[a,b]	2.10±0.09	1.31±0.08	<0.001	6.458

[a]Data are presented as the mean ± SD; [b]comparisons were performed using independent-sample Student's t-test; [c]Data are presented as the median (P_{25}, P_{75}); [d]comparisons were performed using Wilcoxon rank-sum test. AFS, American Fertility Society; BMI, body mass index.

Table II. Comparison of pregnancy methods between the treatment and control groups after hysteroscopy.

Group	Patient number	IVF-ET, n (%)	Natural conception, n (%)	D-value and 95% confidence interval	χ^2 test	
					χ^2 value	P-value
Treatment group	46	38 (82.6)	8 (17.4)	4.7 (-7.9-19.5)	0.468	0.494
Control group	63	55 (87.3)	8 (12.7)			

IVF-ET, *in vitro* fertilization and embryo transfer. The association of dichotomous data between the two groups was assessed using χ^2 test.

Table III. Comparison of pregnancy rates and live birth rates between the treatment and control groups after hysteroscopy.

A, Pregnancy rate

Group	Patient number	Pregnancy, n (%)	No pregnancy, n (%)	D-value and 95% confidence interval	χ^2 test	
					χ^2 value	P-value
Treatment group	46	28 (60.9)	18 (39.1)	5.8 (-12.5-24.1)	0.39	>0.05
Control group	63	42 (66.7)	21 (33.3)			

B, Live birth rate

Group	Patient number	Pregnancy, n (%)	No pregnancy, n (%)	D-value and 95% confidence interval	χ^2 test	
					χ^2 value	P-value
Treatment group	46	19 (41.3)	27 (58.7)	14.3 (-4.5-33.1)	2.16	>0.05
Control group	63	35 (55.6)	28 (44.4)			

The association of dichotomous data between the two groups was evaluated using χ^2 test.

Notably, the pregnancy and live birth rates in the control group were higher than those expected. As the control group didn't use any barrier device, the recurrence rate of adhesion should be higher, but the pregnancy rate of the patients in the control group was not significantly decreased compared with the treatment group through repeated hysteroscopic treatment according to the findings of the present study. This finding was further supported by the study by Deans *et al* (13). In the aforementioned retrospective study, including a total of 154 female patients, the pregnancy and live birth rates were 79.0 and 63.7%, respectively, following repeated hysteroscopic procedures until cavity restoration, without the use of any mechanical barriers (13). The higher pregnancy rate recorded in the control group compared with the treatment group in the present study could be possibly due to the optimization of endometrial proliferation and endometrial receptivity (14). A functional endometrium and an adequate uterine cavity are closely associated with a successful pregnancy (9,10).

Table IV. Obstetric outcomes from live births in the treatment and control groups after hysteroscopy.

Outcome	Number (%)
Live births	54 (49.54)
Cesarean delivery	36 (66.67)
In vitro fertilization and embryo transfer after hysteroscopy	93 (85.30)
Adherent placenta and placenta accreta spectrum	10 (18.82)
Blood transfusion	3 (5.56)
Postpartum hysterectomy	2 (3.70)
Twin live birth	8 (14.81)
Premature birth	5 (9.26)
Neonatal deaths	0 (0.00)

Obstetric outcomes were available for 54 women. A total of 62 neonatal outcomes were reported, including eight pairs of twins.

Although the success rate is associated with the severity of adhesions (15,16), early second-look hysteroscopy and appropriate adjuvant therapy can exert satisfactory effects. A previous RCT has demonstrated that the pregnancy rate in patients with moderate to severe IUAs is improved by adjuvant therapy (5 mg/day transdermal estrogen and 100 mg/day aspirin) after hysteroscopic lysis (17). In the prospective trial by Pabuçcu *et al* (11) the pregnancy and live birth rates were compared between patients who underwent a second-look hysteroscopy at 1 week and a third-look hysteroscopy at 2 months after the first hysteroscopy (Group A) and those who were treated with second-look hysteroscopy 2 months later after the first hysteroscopy (Group B). The results showed that both the pregnancy and live birth rates were higher in Group A compared with those recorded in Group B. However, statistical significance was not reached (11). Therefore, this study suggested that early second-look hysteroscopy may improve the reproductive outcomes of patients with severe IUAs.

The lower live birth rate in the copper-containing IUD group could be due to the following two reasons: Firstly, it has been reported that copper IUDs can induce an inflammatory response in the endometrium (3). Secondly, in the present study, 25 patients in the treatment group and 8 patients in the control group changed their desire for pregnancy after the first hysteroscopy. These patients were not included in the statistical analysis. According to the AFS classification of IUAs (18), a range of live birth rate of 25-50% and a range of pregnancy rate of 50-75% is expected to be achieved in the copper IUD group. Copper-containing IUDs could be an acceptable alternative approach for preventing the recurrence of IUAs, when non-copper IUDs are not available. However, no positive effects on pregnancy and live birth rates were observed. Performing embryo transfer as soon as possible could be a more effective strategy to achieve higher pregnancy and live birth rates after hysteroscopy without the use of barrier devices.

Only a limited number of studies have reported the obstetric outcomes in patients with moderate to severe IUA treated with hysteroscopy (13). In the present study, the placental-related complication rate was 18.82% (10/54). A total of 2 patients (2/54) underwent postpartum hysterectomy due to postpartum hemorrhage caused by placenta accreta spectrum. In addition, twin live birth, premature birth and cesarean section rates of 14.81% (8/54), 9.26% (5/54) and 66.67% (36/54), respectively, were recorded. The aforementioned results were consistent with those reported by Deans *et al* (13). The aforementioned findings suggested that the severity of IUAs could be positively associated with obstetric outcomes. The 2 patients suffering from severe IUAs eventually had their uterus removed.

In conclusion, the results of the current study indicated that copper-containing IUDs had no positive effect on pregnancy and live birth rates in patients with mild to severe IUAs after hysteroscopic adhesiolysis.

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Availability of data and materials

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

PX, YS, JL and BY were responsible for study conception and design, data analysis and first draft revision. HX and QL were responsible for writing the first draft of the article, data analysis and review. SL and EH contributed to data collection and analysis and follow-up. All authors read and approved the final manuscript. PX and BY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of the Affiliated Jinhua Hospital of Wenzhou Medical University (approval no. IRB-20200028-R; Jinhua, China). All patients signed an informed consent form.

Patient consent for publication

All patients provided written informed consent for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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