Am J Transl Res 2022;14(1):484-490
www.ajtr.org /ISSN:1943-8141/AJTR0139743

Original Article

Effect of hysteroscopic adhesiolysis on recurrence, menstruation and pregnancy outcomes in patients with different degrees of intrauterine adhesions

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Received October 11, 2021; Accepted December 2, 2021; Epub January 15, 2022; Published January 30, 2022

Abstract: Objective: To study the recurrence, menstruation, and pregnancy outcome in patients with different degrees of intrauterine adhesions after hysteroscopic adhesiolysis. Methods: From February 2017 to January 2020, 300 patients with intrauterine adhesions were recruited in this study. Patients were divided into group A (mild), group B (moderate) and Group C (severe). All patients underwent hysteroscopic adhesion separation. The uterine cavity was re-examined by hysteroscopy 3 months after surgery to evaluate the uterine cavity morphology, the degree and treatment effect of the intrauterine adhesions, menstrual volume, and pregnancy outcomes after 2 years. Results: Compared to group A, the reconstruction rates of group B and C were lower, and group B was significantly higher than group C. The re-adhesion rate of group C was significantly higher than that of group A and group B, but no significant differences were observed between group A and group B. Furthermore, the efficacy of surgical treatment was evaluated. The treatment effect of group B and group C was not as obvious as that of group A, and group C was worse. The degree of intrauterine adhesions was negatively correlated with pregnancy rate and live birth rate of the fetus. Before treatment, there were significant differences in endometrial vascular index (EVI), blood flow Index (FI), endometrial volume (EV), and vascular blood flow index (VFI) among the three groups of patients with different degrees of adhesion. As the degree of adhesion increased before treatment, blood flow decreased. Surgery significantly improved the clinical symptoms of the three groups of patients. Moreover, the recovery of patients in group A was the best, followed by group B, and group C had the worst recovery. Conclusion: The treatment effect and prognosis of patients were related to the degree of intrauterine adhesions before treatment. As the degree of intrauterine adhesions increased, the treatment effect and prognosis of patients became worse, and intensive treatment was needed. (Chinese Clinical Trial Registry, trial number ChiCTR1700026770, trial URL: http://www.chictr.org.cn/).

Keywords: Hysteroscopic adhesions separation, intrauterine adhesions, different degrees, recurrence, menstruation, pregnancy outcome

Introduction

Uterine adhesion is a syndrome in which the endometrial basement membrane is damaged by surgery, infection and other causes, which leads to irregular menstruation, amenorrhea, and other symptoms. It was described by Asherman in 1948 as Amenorrhea Traumatica [1]. Severe cases can lead to fertility disorders, such as infertility and recurrent miscarriage, which seriously affect women's fertility and psychology [1, 2]. Studies have shown that the vast majority of intrauterine adhesions are caused by curettage [3]. In recent years, the occurrence of intrauterine adhesions has increased due to intrauterine surgery for myoma, septum and bicornuate uterus [4]. Most patients with intrauterine adhesions are asymptomatic and require treatment only when accompanied by pain, bleeding or impaired fertility [5]. Currently, hysteroscopic adhesion lysis is the most common and effective option in clinical treatment of uterine adhesions. Hysteroscopic adhesion lysis can greatly restore the normal volume and shape of uterus [6]. Studies have found that the recurrence rate was 3% to 24% after surgery [7-9]. The highest rates reach 20% to 63% [8, 10]. This study aimed to investigate the effect of uterine adhesion lysis on patients with different degrees of uterine adhesions and to improve the clinical use of this method.

Methods

Information

From February 2017 to January 2020, 300 patients with intrauterine adhesions were selected as research subjects. According to the degree of intrauterine adhesions, they were divided into group A (mild), group B (moderate), and Group C (severe). Intrauterine adhesions involved 1/3, 1/3-2/3, and more than 2/3 of the uterine cavity in group A, B, and C, respectively. There were 100 patients in each group. This study was approved by the ethics committee of Jiangxi Maternal and Child Health Hospital (Approval number: 201707019).

Inclusion criteria: 1) women in need of childbearing (≥18 years old); 2) patients with intrauterine adhesions confirmed by hysteroscopy; 3) patients who underwent intrauterine adhesiolysis for the first time; 4) patients with normal genital development; 5) patients with normal sex hormone levels; 6) patients who provided informed consent.

Exclusion criteria: 1) patients in the acute stage of genital tract infection; 2) patients with uterine malformation and lesions; 3) patients with pelvic inflammation; 4) patients with irregular vaginal bleeding of unknown cause; 5) patients with ovarian, pituitary or hypothalamic amenorrhea; 6) patients with infertility or partner infertility caused by other causes; 7) patients with combined with severe organic dysfunction of heart, lung, liver, or kidney; 8) patients with communication disorders and mental disorders; 9) patients without follow-up conditions.

Surgical methods

All subjects underwent hysteroscopic adhesiolysis 3-7 days after the end of the menstruation. For amenorrhea patients, hysteroscopic adhesiolysis was performed at any time. All patients were injected with 200 mg of misoprostol (Beijing Zizhu Pharmaceutical Co., Ltd., GYZZ H20000668) through the posterior vaginal fornix the night before operation and the next morning to soften the cervix. Unified hysteroscopy (STORZ, Germany) was used in the operation. The patient was in the bladder lithotomy position during the operation. The cervix was dilated by a cervical dilator and a hysteroscope was placed in the cervix to observe intrauterine adhesions. The needle electrode was advanced to bluntly separate the adhesions until the uterus returns to its normal shape and size, the opening of bilateral fallopian tubes was clearly visible, and both uterine corners were visible in the internal cervical orifice. All patients were implanted with an intrauterine device (Wuhan Fahrenheit Oriental Trade Co., Ltd.) and sodium hyaluronate (Shandong Ph.D. Lunfreda Pharmaceutical Co., Ltd., Approval number: GYZZ H10960136) was injected with 2 mL to prevent recurrence of adhesions. Routine antibiotic anti-infection treatment was adopted.

Observation index

The uterine morphology of patients with pretreated intrauterine adhesions was observed by two-dimensional ultrasound. Three-dimensional ultrasound diagnostic equipment (GE Voluson EXPERT type, probe frequency: 3-9 MHz) was used to evaluate the patient's uterine status before and 3 months after surgery. The patient's uterine cavity position, shape, lesion range, echo intensity, and other indicators were recorded. The VACOL analysis software that comes with the ultrasound diagnostic instrument was used to evaluate the endometrial contour, and the following index values were recorded: endometrial vascular index (EVI), blood flow Index (FI), endometrial volume (EV), vascular blood flow index (VFI) and the change values of each index before and after surgery.

All patients were examined at 3 months after intrauterine adhesion separation. Observation indicators were as follows: 1) Reconstruction of uterine cavity morphology, including completely normal, basically normal, abnormal and re-adhesions, was evaluated. The reconstruction rate = (completely normal cases + basically normal cases)/the total number of cases * 100%. 2) The degree of uterine adhesion and the treatment effect: three months after operation, the treatment effect was judged by hysteroscopy results. Cure: The shape and size of the uterine cavity were normal, the oviduct opening was clear, and the menstruation was normal. Improvement: Intrauterine adhesion decreased by grade 1-2, the menstruation improved compared with before treatment, but not to the normal level. Ineffective: no significant change or aggravation of intrauterine cavity adhesion compared with before operation,

Table 1. General data

	group A	group B	group C	*F*	*P*
Age (years old)	34.29±3.27	33.24±3.65	33.83±3.26	2.399	0.092
BMI (kg/m^2)	23.85±2.39	24.02±2.08	23.62±2.18	0.817	0.442
Miscarriage history (n)	2.6±0.5	2.5±0.5	2.5±0.5	1.338	0.264
Curettage history (n)	2.7±0.46	2.7±0.52	2.58±0.60	1.710	0.182
Pregnancy history (n)	2.5±0.5	2.5±0.6	2.6±0.5	1.163	0.314
duration of disease (months)	15.32±4.11	14.94±4.35	15.14±4.05	0.207	0.812

Table 2. Comparison of uterine cavity reconstruction among the 3 groups

	Completely normal	basically normal	abnormal	Reconstruction rate (%)
group A	30 (30.0)	58 (58.0)	12 (12.0)	88 (88.0)
group B	28 (28.0)	51 (51.0)	21 (21.0)	79 (79.0)$^{\#}$
group C	15 (15.0)	49 (49.0)	36 (36.0)	64 (64.0)$^{\#,*}$
χ^2	7.205	1.792	16.601	16.601
P	0.027	0.408	<0.001	<0.001

Note: Compared with group A, $^{\#}P<0.05$; Compared with group B, $^{*}P<0.05$; Chi-square test was used to compare the two groups.

Table 3. Comparison of the degree of intrauterine adhesion and treatment efficiency among the 3 groups

	Adhesion rate (%)	Cure	Effective	Ineffective	Effective rate (%)
group A	10 (10.0)	26 (26.0)	49 (49.0)	25 (25.0)	75 (75.00)
group B	18 (18.0)	15 (15.0)	45 (45.0)	40 (40.0)	60 (60.00)$^{\#}$
group C	35 (35.0)	9 (9.0)	32 (32.0)	59 (59.0)	41 (41.0)$^{\#,*}$
χ^2	19.650	10.704	6.486	23.946	23.946
P	<0.001	0.005	0.039	<0.001	<0.001

Note: Compared to group A, $^{\#}P<0.05$; Compared to group B, $^{*}P<0.05$; Chi-square test was used to compare the two groups.

and the menstruation did not recover. Effective rate = (number of cured cases + number of improved cases)/total number of cases * 100%. 3) Menstrual volume (mL). 4) Pregnancy and pregnancy outcomes: pregnancy was recorded at 1-year follow-up after operation, and pregnancy outcomes were followed up for 2 years after operation.

Statistical analysis

SPSS 19.0 software was used for data analysis, and GraphPad Prism 8 software was used for image rendering. The measured value was presented by mean ± SD, and One-way ANOVA was adopted for the comparison among the three groups, and LSD-t test was used for the pairwise analysis. Paired t test was used to compare before and after treatment within the group. The counted data were expressed as n (%) and Chi-square test was used for comparison between two groups. $P<0.05$ was considered significant.

Results

Comparison of general conditions among three groups of patients

One-way ANOVA was used to compare general data among the three groups. As shown in **Table 1**, the patients in the 3 groups were comparable in terms of age, body mass index (BMI), history of miscarriage, history of curettage, history of pregnancy, and course of disease ($P>0.05$).

Comparison of uterine cavity morphology reconstruction among the three groups

The Chi-square test was used to compare uterine cavity reconstruction rates among three groups or two groups. As shown in **Table 2**, the uterine cavity morphological reconstruction rates in groups A, B, and C were 88.0%, 79.0% and 64.0%, respectively. The reconstruction rate of group B and C was lower than that of group A (P<0.05), and the rate of group C was significantly lower than that of group B (P<0.05).

Comparison of degree of intrauterine adhesions and therapeutic effect among three groups

The Chi-square test was used to compare degree of intrauterine adhesions and therapeutic effect among the 2 or 3 groups. As shown in **Table 3**, the higher the degree of intrauterine adhesions in patients, the higher the incidence

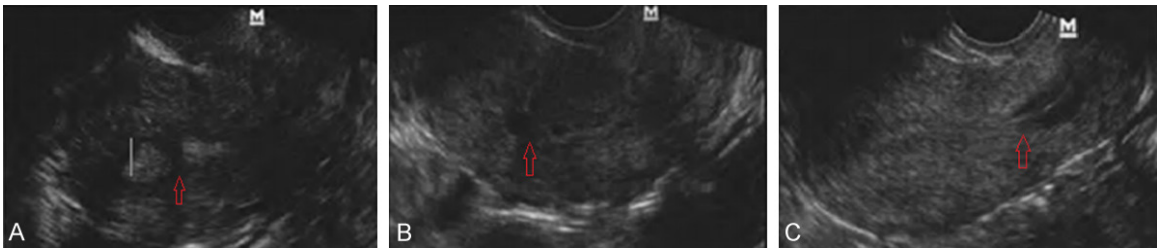

Figure 1. Two-dimensional ultrasound imaging images of patients with intrauterine adhesions. A. The endometrium of the uterine cavity was interrupted, banded, and hypoechoic; B. The thickness of the endometrium of the uterine cavity was uneven, banded echo, and localized effusion; C. The endometrium of the uterine cavity was unclear.

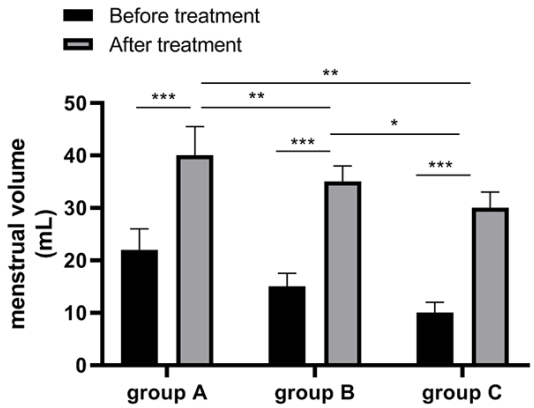

Figure 2. Differences of menstrual volume among the 3 groups. *P<0.05, **P<0.01, ***P<0.001, Paired t test was used to compare before and after treatment within the group, LSD t test was used to compare the two groups.

of intrauterine re-adhesion. The adhesion rate of group C (35%) was dramatically higher than that of group A (10.0%) and group B (18.0%) (all P<0.05). Furthermore, the effect of surgical treatment was evaluated, as shown in **Table 3**. Among the three groups, patients in group A exhibited the best treatment effect, but group C showed the worst treatment effect, and the difference between the three groups was significant (P<0.05).

Comparison of improvement of menstrual volume among the three groups

As shown in **Figure 1A-C**, in Type I, the endometrium of the uterine cavity is interrupted, banded hypoechoic. In Type II, the thickness of the endometrium of the uterine cavity is uneven, banded echo, and localized effusion. In Type III, the endometrium of the uterine cavity is unclear. Three groups of patients with thin and narrow uterine cavity have different thickness of the endometrium (group A > group B > group C).

Table 4. Comparison of pregnancy and pregnancy outcomes among the 3 groups

	Pregnancy rate (%)	Live birth rate (%)
group A	88 (88.0)	47 (47.0)
group B	61 (61.0)#	22 (22.0)#
group C	49 (49.0)#	13 (13.0)#
χ^2	35.561	31.249
P	<0.001	<0.001

Note: Compared to group A, #P<0.05; Chi-square test was used to compare the two groups.

As shown in **Figure 2**, menstrual volume also improved significantly after treatment (P<0.05), and the menstrual volume of patients in groups A and B was significantly higher than that of group C (P<0.05).

Comparison of pregnancy outcome among three groups

After 1 year of treatment, the degree of intrauterine adhesions of the patients in the 3 groups gradually increased, and the pregnancy rate therefore gradually decreased, and these were 88.0%, 61.0%, and 49.0%, respectively. The live birth rates of the three groups were 47.0%, 22.0%, and 13.0%, respectively. The pregnancy rate and live birth rate of patients in group A were significantly higher than those of groups B and C (P<0.05, **Table 4**).

Comparison of endometrial blood perfusion in the three groups

As shown in **Table 5**, the EV, VI, FI, and VFI of the three groups of patients after treatment were different from those before treatment (P<0.05). As the degree of adhesion increased

Table 5. Comparison of endometrial blood flow in EV, VI, FI, and VFI before and after surgery in the three groups

	EV		VI		FI		VFI	
	Preoperative	Postoperative	Perioperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
group A	2.56±1.07	4.12±0.87*	2.74±1.68	3.98±2.05*	23.88±2.92	25.67±5.42*	0.87±0.44	1.25±0.35*
group B	2.04±1.81a	3.41±0.78a,*	1.78±1.63a	3.05±1.89*,a	21.13±3.43a	23.78±4.32*,a	0.72±0.56a	1.10±0.41*,a
group C	1.17±0.36a,b	3.01±0.57*,a,b	0.72±0.50a,b	2.74±1.75*,a,b	16.62±4.21a,b	20.54±4.65*,a,b	0.19±0.13a,b	0.98±0.52*,a,b
F	26.404	2.567	22.959	3.512	25.665	2.156	20.769	4.354
P	<0.001	0.042	<0.001	0.035	<0.001	0.048	<0.001	0.005

Note: Compared to Preoperative, *P<0.05; Compared to group A, aP<0.05; Compared to group B, bP<0.05; Paired t test was used to compare before and after surgery within the group, LSD-t test was used to compare two groups.

before treatment, blood flow decreased. After surgical treatment, the three groups of patients improved significantly compared to before treatment (P<0.05). Moreover, the postoperative recovery of adhesion degree was better in group A than group B and C, and the improvement in group B was better than group C (P<0.05).

Discussion

The symptoms of intrauterine adhesions can range from asymptomatic to irregular menstruation. The symptoms are sometime not obvious, so it is difficult to calculate an accurate incidence rate. The incidence of intrauterine adhesions is high in China, and seriously affects female reproductive health [11]. With the emergence of iatrogenic endometrial injury and excellent diagnostic techniques, the diagnosis rate of intrauterine adhesions has also increased [12]. Intrauterine adhesions can be divided into degrees I, II, and III according to the severity of the adhesions. Patients with grades II and III intrauterine adhesions have more severe clinical symptoms and higher risk of recurrence [13, 14]. Hysteroscopy is the preferred method for diagnosis and treatment of patients with intrauterine adhesions [15]. The operation can easily and quickly separate and resect the adherent tissues, which is beneficial to the recovery of the menstrual cycle [12]. Hysteroscopic surgery is widely used in the clinical treatment of uterine adhesions [16]. However, the postoperative recurrence rate is still high, reaching 20%-60% [8, 10-17], The increase in the number of intrauterine operations will aggravate intrauterine adhesions [18]. Therefore, it is essential to reduce postoperative adhesions. The results of this study proved that the more severe the uterine cavity adhesion, the lower the recovery rate of uterine cavity morphology reconstruction, and the higher the incidence of postoperative re-adhesion. In addition, patients with intrauterine adhesions in group A had better results of uterine cavity reconstruction and lower incidence of postoperative re-adhesion, indicating that the therapeutic effect of hysteroscopic adhesiolysis was negatively related to the degree of intrauterine adhesions.

The endometrium is one of the important components of the uterus. The endometrium can reflect the degree of endometrial hyperplasia. The degree of endometrial injury caused by intrauterine adhesions is significantly related to menstruation and pregnancy [19-21]. Previous studies indicated that a reduction in the thickness of the endometrium affects the pregnancy rate and implantation rate of fertilized eggs [22], about 31% of patients with decreased menstruation and 37% with amenorrhea [3]. This study found that the menstrual volume of the three groups of patients increased significantly after treatment. There were significant differences among the three groups, indicating that the intrauterine adhesions were significantly improved.

Previous studies demonstrated that the degree of intrauterine adhesions was negatively correlated with the postoperative prognosis, and the high degree of adhesions led to an increase in the probability of reoperation [7-23]. Postoperative reproductive function has a worse prognosis than menstruation or other clinical symptoms, with pregnancy rates ranging from 44% to 93% [24, 25]. The mechanism of intrauterine adhesions affecting pregnancy may be affected by insufficient endometrium, reduced delivery of steroids to endometrial tissue, and changes in endometrial biochemical environment [26-29]. In addition, factors such

as the number of occurrences of intrauterine adhesions, the degree of adhesions and the effect of surgery will also affect the pregnancy of patients with intrauterine adhesions. Before treatment, there were significant differences in VI, FI, EV, and VFI among the three groups of patients with different degrees of adhesion. As the degree of adhesion increases before treatment, blood flow decreases. After surgical treatment, the three groups of patients all improved greatly compared with before treatment. However, the postoperative recovery of the adhesion degree in group A was better than that of groups B and C, and the improvement of group B was better than that of group C. With the increase of severity, the patient's treatment effect is worsened, similar to the results of current research [30, 31]. Since this study was a single-center study, patients in other centers were not compared, and the results may have some limitations. In the future, we will collect data from other centers for comparison to improve the reliability of our conclusions.

In summary, the therapeutic effect and prognosis of patients with intrauterine adhesions are related to the degree of intrauterine adhesions. As the degree of intrauterine adhesions increases, the treatment effect and prognosis of patients become worse, and more treatment may be required.

Disclosure of conflict of interest

None.

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