Clinical characteristics and reproductive outcome following hysteroscopic adhesiolysis of patients with intrauterine adhesion - a retrospective study

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Summary

The authors performed a retrospective clinical analysis of 153 patients with intrauterine ashesion (IUA) who underwent hysteroscopic adhesiolysis. A follow-up office hysteroscopy was performed in all cases after three months. On follow-up hysteroscopy, 22 patients showed reformation of adhesions and required a repeat procedure. The primary risk factor for IUA was uterine curettage associated with pregnancy termination. The follow-up study revealed that the rate of pregnancy after IUA treatment was 51%. The conception rate in women who had reformation of IUA was significantly lower than that of women who had a normal cavity following adhesiolysis. Therefore the authors conclude that prevention is more important than therapy in IUA. Increasing education about avoiding curettage is necessary to reduce the incidence of IUA. Outreach is particularly important for older women with less education. However, hysteroscopic adhesiolysis for IUA is a safe and effective method of choice for restoring menstrual function and fertility.

Key words: Intrauterine adhesion; Hysteroscopic adhesiolysis; Reproductive outcome; Adhesion prevention.

Introduction

It has been more than one century since Heinrich Fritsch first described intrauterine adhesion (IUA) caused by trauma to the uterine cavity [1]. In 1948, Joseph G. Asherman published a series of papers to describe the frequency, etiology, symptoms, and roentgenologic picture of this condition, and Asherman syndrome has been used to describe the disease ever since [2]. IUA is a consequence of trauma to the endometrium, which causes partial or complete obstruction in the uterine cavity and/or the cervical canal, resulting in conditions such as menstrual abnormalities, infertility, recurrent pregnancy loss, fetal intrauterine growth retardation, abnormal placenta development, and other complications related to conception. Universally, the incidence of IUA is increasing, mainly from curettage during induced, incomplete, or missed abortions, postpartum hemorrhage, and genital tuberculosis [3]. Any operation in the uterine cavity can cause IUA, therefore only necessary operations should be performed. Currently, hysteroscopy is the method of choice to diagnose, treat, and follow patients with intrauterine adhesions. In China, IUA incidence, detected by hysteroscopy, has increased and presents with diverse manifestations. The treatment of severe IUA is still puzzling for clinicians. Bearing in mind the triad of poverty, ignorance, and disease, and the vicious cycle thus generated [4], this paper aims to outline the clinical characteristics of women presenting with IUA and their reproductive outcome for better prevention, diagnosis, and treatment of IUA.

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Materials and Methods

The authors retrospectively enrolled the patients with IUA who attended the in-patients of minimally invasive center of Obstetrics and Gynecology Hospital of Beijing during a six-year period between June 2005 and June 2011. The inclusion criterion for this study was hysteroscopically diagnosed IUAs. In all patients, a comprehensive infertility workup was performed including: a tubal patency test, pelvic ultrasonography, husband semen analysis, and serum hormone measurements (FSH, LH, prolactin, estradiol, progesterone, and androgen) on the second to fifth day of the cycle or at a randomly chosen time in patients with amenorrhea. Any patients with abnormal test results that may have been responsible for reproductive failure were excluded from the study.

Hysteroscopic adhesiolysis was performed under general anesthesia by an operator experienced with operative hysteroscopic procedures under laparoscopy or ultrasound using a monopolar knife. At the end of the adhesiolysis, a T-shaped intrauterine contraceptive device (IUCD) was inserted as a stent into the uterine cavity and hormone treatment was begun, consisting of estradiol valerate at a dose of four mg/day for 21 days, with the addition of medroxyprogesterone acetate at a dose of ten mg/day in the last ten days of estrogen treatment. Antibiotics were used after the operation. After three months, a second follow-up hysteroscopy was performed in the early proliferative phase of the menstrual cycle in those patients who were menstruating. If reformation of adhesions had occurred, a repeat adhesiolysis procedure was performed during the follow-up procedure. The IUCD was removed during the follow-up hysteroscopy once the presence or absence of adhesion had been determined. If a repeat adhesiolysis procedure was performed, a second IUCD was inserted into the uterine cavity and hormone treatment was repeated. All patients had a follow-up examination and 22 patients required a second adhesiolysis. No patient underwent more than two procedures. In patients who remained amenorrheic in spite of hormonal treatment, a diagnostic hysteroscopy was also performed three months after the initial hysteroscopic adhesiolysis. When adhesions were absent at

Table 1. — *Subject characteristics of patients with IUA.*

Item	Mininum	Maximum	mean	std. Deviation
Age (years)	22	43	32	4.4
Education (years)	9	20	13.9	2.9
Gestation (n.)	0	7	2.2	1.6
Parity (n.)	0	5	0.2	0.5
Operation time (minutes)	10	120	38.9	21.5

Predisposing factor in the patients of IUA	number (n)	Percentage (%)
Trauma to a gravid uterine cavity		
Dilatation and curettage	132	86.6
Evacuation for hydatidiform mole	2	1.3
Infection after labor	2	1.3
Trauma to non-gravid endometrium		
Polypectomy	1	0.65
Resection of septum	1	0.65
Myomectomy	1	0.65
Unexplained	14	9.2

the second hysteroscopy, the patients were encouraged to resume their efforts to conceive.

A follow-up by telephone was conducted during July 2012 to learn the reproductive outcome and the amount of time between operation and conception in the enrolled patients. The study included 153 patients. According to the American Fertility Society (AFS) score system published in 1988 [5], the patients were divided into mild, moderate, and severe groups based on the severity of IUA.

Statistical analysis was performed using SPSS 18.0 version software. For continuous variables, t tests were used for between group comparisons and were expressed as means ± standard deviation (SD); for categorical variables; $\chi 2$ tests were used for between group comparisons. The α-level was set at 0.05.

Results

The mean age of patients with IUA was 32.0 years, with a range between 22 and 43 years of age. The mean time of gestation was 2.2, and the parity was 0.2. The mean duration of education was 13.4 years, and the mean duration of operation time was 38.9 minutes (Table 1). The most significant contributing factor to an IUA diagnosis was a history of dilatation and curettage for uterine evacuation, either for a spontaneous or induced abortion or postpartum haemorrhage. Other contributing factors included: a history of polypectomy, resection of the septum, and myomectomy. No apparent predisposing factors were found in 14 of the patients enrolled in the study (Table 1). Based on their reproductive outcome, the patients were divided into a group that successfully conceived and a group that did not successfully conceive. The patients able to conceive were significantly younger (31.0 *vs*. 32.9 years, $p = 0.038$) than those unable to conceive and more educated (14.3 *vs*. 13.4 year, $p = 0.001$). There was no significant difference in the time of gestation or parity and the operation duration between the two groups.

Table 2. — *Clinical presentation*.*

Presentation	Number	Percentage
Primary infertility	18	11
Secondary infertility	32	21
Secondary amenorrhea	15	10
Hypomenorrhea	73	48
Abnormal mass in uterine cavity	5	3
Malformation of uterine	7	5
Lower abdominal pain	2	1
Ectopic pregnancy	1	1

* more than one kind of presentation in some patients.

Table 3. — *The relationship between the main manifestation and disease score.*

Classification	Number n (%)	Abnormal menstruation n (%)	Infertility n (%)	*p*
Mild	10 (7.2)	4 (40)	6 (60)	0.017#
Moderate	78 (56.5)	34 (43.6)	44 (56.4)	0.007*
Severe	50 (36.2)	40 (80)	10 (20)	

the mild group compared with the severe one
* the moderate group compared with the severe one

Patients presented with diverse clinical manifestations are shown in Table 2. There were 13 (8.5%) patients in the mild degree group, 86 (56.2%) in the moderate group, and 54 (35.3%) patients in the severe degree group. Menstrual abnormalities and infertility were present in 90% of cases overall. Among the 13 patients in the mild group, four (40%) patients presented with abnormal menstruation and six (60%) with infertility. In the moderate and severe groups, the number of patients presenting with abnormal menstruation or infertility were 44 (43.6%) and 34 (56.4%), and 40 (80%) and ten (20%), respectively (Table 3). In the severe group the main clinical presentation was abnormal menstruation, and in the moderate and mild groups it was infertility.

A follow-up by telephone was conducted to determine the menstrual pattern, conception rate, time between treatment and conception, and the reproductive outcome for each patient. The numbers of women with amenorrhea, hypomenorrhea, or normal menstruation before and after surgery were 15/115/23 and 2/74/77, respectively. Amenorrhea and hypomenorrhea prior to surgery were improved in 67 out of 130 patients (51.5%). Table 4 shows the correlation between conception and menstrual pattern before and after adhesiolysis.

The conception and reproductive outcomes of all 153 patients after hysteroscopic adhesiolysis are given in Table 5. Among 153 women, 78 (51%) achieved pregnancy. In the 22 patients with reformed intrauterine adhesions at the follow-up hysteroscopy, only four conceptions (18.2%) occurred despite further adhesiolysis. Among 131 women with normal cavities at the follow-up hysteroscopy, 74 conceptions (56.5%) occurred ($p < 0.05$). The mean time in-

Table 4. — Menstrual pattern before and after hysteroscopic adhesiolysis and relationship to conception rate.

Menstrual pattern before treatment (n = 153)	Menstrual patterns after treatment			
	Amenorrhea (*n* = 2)	Hypomenorrhea (n = 74)	Normal menses (n = 77)	Conception rate (%)
Amenorrhea (n = 15)	0/2	4/10	1/3	5/15 (33.3%)
Hypomenorrhea (n = 115)	0	29/63	30/52	59/115 (51.3%)
Normal menses (n = 23)	0	0/1	14/22	14/22 (63.6%)
Conception rate (%)	0	33/74 (44.6%)	45/77 (58.4%)	78/153 (51.0%)

Table 5. — Conception and reproductive outcomes in 153 patients after hysteroscopic adhesiolysis with different grades of adhesion.

No.	Variable	Mild (*n* = 13) (%)	Moderate (*n* = 86) (%)	Severe (*n* = 54) (%)
1	Conception	7/13 (53.8)	49/86 (60)	21/54 (38.9)
2	Spontaneous miscarriage	1/7 (14.3)	6/49 (12.2)	3/21 (14.3)
3	Ongoing pregnancy	3/7 (42.9)	13/49 (26.5)	2/21 (9.5)
4	Live birth	3/7 (42.9)	30/49 (61.2)	16/21(76.2)

terval between treatment and conception was 15.9 months. Of the 78 pregnancies, 49 (62.8%) were live births, ten (12.8%) had spontaneous miscarriages, and 19 (24.4%) were pregnant at the time of follow-up (three pregnancies were less than 12 weeks and 16 pregnancies were more than 12 weeks at the time of follow-up). Forty women underwent cesarean sections to give birth; six of those patients had abnormal placentas. In those six cases, one case was placental adhesion and two cases were placental accreta, both patients had postpartum hemorrhaging, and one patient lost her uterus. The remaining three cases were placental previa in which one case achieved termed birth, while the other two cases were preterm deliveries at 35 weeks and 32 weeks, respectively. Fourteen patients attempted assisted reproductive techniques, and of those, five patients had term births and two patients had abortions. The mean time interval between operation and conception in these cases was 29 months.

Discussion

The patients enrolled in the study generally had lower levels of education and were older women. IUA presentation was more severe the more times the patients had undergone curettage and the lower their education level. It is possible to educate women about contraception to avoid unplanned pregnancy and reduce incidence of curettage. In China, attitudes and behavior are changing, on one hand sex is becoming more open and sexual behavior is increasing, and on the other hand unplanned pregnancy is increasing. Women also delay planned conception because of the rapid pace of life and the competition of work; both of which increase the opportunity of curettage for accidental conception.

The main complaint of patients with IUA was abnormal menstruation or infertility, and there was some relationship between the severity score and clinical manifestation. This relationship may have been caused by the classification criteria. The AFS score emphasizes the pattern of menstruation but leaves out the symptom of infertility. Therefore, in infertility patients, it is desirable to perform hysteroscopy to evaluate the capacity of the reproductive system. For patients who had normal menstruation, it was difficult to explain the occurrence of IUA. It may have been caused by chronic reproductive system infection or latent tuberculosis infection. Furthermore, chronic tuberculosis is difficult to diagnose. Another symptom is infertility caused by obstruction of the tubal ostia or endocervix. Patients can have subclinical recurrent abortion caused by the smaller uterine cavity size, poor endometrial receptivity, the defect of endometrium, myometrial fibrosis, and reduced uterine blood flow [6]. The present analysis supports that trauma to a gravid uterine cavity is the main cause of Asherman's syndrome [7]. One of the possible explanations for the gravid uterus being a major predisposing factor to Asherman's syndrome is the low estrogen status at the time of the operation or immediately following.

Modern treatment of IUA has focused on two areas: the first is the actual management of the adhesions, and the second is preventing adhesion reformation. In severe cases, it may be necessary to perform concurrent ultrasonography to facilitate passage through the endocervical canal and internal os into the cavity. Simultaneous laparoscopy may also be valuable for guiding adhesiolysis. The most effective therapy is combination of post-hysteroscopical IUD and administration of artificial menstruation period [6]. Different techniques for hysteroscopic adhesiolysis have been described. Hysteroscopic scissors [8] or laser treatment [9] has been used to divide adhesions. Hysteroscopic resection with a monopolar probe was also found to be efficient [10, 11]. In the present study, the authors used a monopolar knife to divide adhesions, which is effective, safe, and less expensive in a limited resource setting. The concurrent laparoscopy in this study to confirm the tubal patency and to rule out other pelvic pathology also helped to know the end point of adhesiolysis by observing the transillumination. There were no cases of uterine perforation in this series, which

may be due to concurrent laparoscopy during the procedure. There were two cases (1.3%) of complication of transurethral prostatic resection (TURP) in 153 patients. After the administration of sodium chloride, furosemide, and aminophylline, the symptom was eliminated. The mean duration of the hysteroscopic adhesiolysis procedure is reported to vary between ten and 45 minutes [12, 13]. In the present series, the mean operating time was 38.9 minutes, and the difference in the mean operating time for mild, moderate, and severe Asherman's syndrome was not statistically significant.

Serum from the areas of freshly dissected scars can promote scar reformation. Thus, a non-reactive uterine stent is placed to keep the uterine walls apart during the initial postoperative healing phase. Polishuk *et al.* [14] reported that by following adhesiolysis with IUD placement, the rate of adhesion reformation was only 10%. In contrast, in a prior series of their patients treated without an IUD, the recurrence rate was >50%. Several other methods for reducing re-formation of adhesions have been advocated, including the use of amnion around a balloon catheter, the use of a spray gel adhesion barrier, and early intervention after electrocautery lysis of adhesions [6, 15, 16]. However, none of these methods have sufficient data to recommend them at this time. Therefore, in the present study the authors used an inert IUD kept in situ for 90 days and reported no complications. A combination of estrogen and progestin therapy has been successfully used [17, 18]. However, they preferred giving estradiol valerate at a dose of four mg/day for 21 days, with the addition of medroxyprogesterone acetate at a dose of ten mg/day in the last ten days of estrogen treatment.

It has been reported that improvement of menstrual flow after hysteroscopic adhesiolysis ranges from 52.4 to 74.2% [12]. In the present series, the improvement of menstrual function was 70.6% (53 out of 75), which was similar to a recent report [17]. The authors also found that there was no significant association between conception rate after adhesiolysis and preoperative menstrual pattern. Extensive review articles consistently find the same numbers, with live birth rates of 32 to 76%. In most series, the more extensive the adhesions, the lower the pregnancy and live birth rates. For those patients who achieve pregnancy, there is a significant risk of complications including placenta accreta [16]. Yu *et al.* [17] in a recent study of 85 patients with 109 operative procedures, found that women who remained amenorrheic had a significantly lower chance of conception; 18.2% versus 50%. Similarly, the conception rate for women with a normal cavity at follow-up hysteroscopy was 59.1% versus 11.8% for those who had re-formation of adhesions. In the present analysis, 78 (51%) patients out of 153 patients became pregnant. Among those, ten had abortions, and 49 patients had live deliveries; 16 patients were more than 12 weeks pregnant at follow-up. The mean time interval between operation and conception was 15.9 months. Of the live deliveries, the cesarean rate amounted to 81.6%. Patients with more severe adhesions had a higher cesarean rate. Women who successfully became pregnant were younger and more educated. Therefore, it is important to increase outreach to women with a lower education levels and provide pregnancy planning at younger ages. Furthermore, for patients with IUA, it is essential to emphasize supervision during pregnancy to avoid complications.

Re-adhesion after adhesiolysis is the main factor which effects the outcome of reproduction in IUA patients [17]. The mechanism of adhesion formation after operation in the abdominal cavity has been reported [17, 19]. However, research in the field of operations in the uterine cavity is rarely seen. It is unknown which cytokines or genes take part in the formation of uterine adhesions. Molecular research in wound healing of the skin may supply some hints. This work indicates that miRNA plays an important role in all stages of wound healing of skin [20]. Chronic wounds are a major health burden and developing newer and more effective treatments has therefore become a necessity. Knowledge of miRNA function in the regulation of wound healing and developing improved miRNA modulation techniques in the skin will help translate this knowledge into more effective therapies.

In conclusion, IUA was readily seen in the women with lower education levels. Because of the burden of life and work, women may delay planned pregnancies. So it is essential to educate woman about the hazards of curettage and the decline of reproductive ability with aging. Hysteroscopic adhesiolysis is a safe and effective procedure for the restoration of normal cavity and menstruation. The choice of anti-adhesions still requires large, rigorous, and multi-center research trials to verify best practices. Future research should focus on the prevention of re-adhesion after adhesiolysis and supervision for pregnant woman after adhesiolysis.

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