

Factors affecting reproductive outcome of hysteroscopic adhesiolysis for Asherman's syndrome

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Objective: To evaluate the outcome of hysteroscopic adhesiolysis in women with Asherman's syndrome.

Design: Retrospective clinical study.

Setting: Hysteroscopic center of Fuxing Hospital in Beijing, China.

Patient(s): Patients with Asherman's syndrome who presented with a history of infertility or recurrent pregnancy loss were included in the study.

Intervention(s): The adhesions were divided hysteroscopically by electrode needle or loop under direct vision. A second look hysteroscopy was performed after 3 months.

Main Outcome Measure(s): The menstrual pattern, the time interval to conceive, and the reproductive outcome were recorded.

Result(s): A total of 109 operative procedures were performed in 85 cases. Uterine perforation occurred on one occasion (0.9%). After hysteroscopic adhesiolysis, the chances of conception in women who remained amenorrheic (2 out of 11; 18.2%) were significantly lower than those who continued to have menses (37 out of 74; 50%). At second look hysteroscopy, the conception rate in women who had reformation of intrauterine adhesions (2 out of 17; 11.8%) was significantly lower than that of women who had a normal cavity (26 out of 44; 59.1%).

Conclusion(s): The outcome of hysteroscopic adhesiolysis for Asherman's syndrome is significantly affected by recurrence of intrauterine adhesions. Further research in Asherman's syndrome should be directed toward reduction of adhesion reformation with a view to improving outcome. (Fertil Steril® 2008;89:715–22. ©2008 by American Society for Reproductive Medicine.)

Key Words: Hysteroscopic adhesiolysis, intrauterine adhesions, Asherman's syndrome, conception

Asherman's syndrome has been reported and studied for more than a century. This disease occurs mainly as a result of trauma to a gravid or nongravid uterine cavity, and patients usually present with amenorrhea or hypomenorrhea, infertility, or recurrent pregnancy loss. Despite the wide use of diagnostic and operative hysteroscopy, the management of Asherman's syndrome remains challenging.

Many studies have reported on the reproductive outcome after treatment of Asherman's syndrome (1–9). However, very few analyzed the reproductive outcome systematically according to the various types of presentation, the severity of intrauterine adhesions, the menstrual pattern after surgery, and whether or not adhesions recurred after adhesiolysis.

The present retrospective study analyzes the outcome of hysteroscopic adhesiolysis in 85 women with Asherman's syndrome who presented with a history of infertility or recurrent pregnancy loss. The possible factors affecting reproductive outcome, menstrual patterns before and after treatment, severity of the disease, and reformation of adhesions are an-

alyzed. The time interval between treatment and conception also is examined.

MATERIALS AND METHODS

Subjects

The study was carried out at the hysteroscopic center of Fuxing Hospital in Beijing, China. Institutional Review Board approval was obtained before the study. From January 1998 to June 2005, a total of 122 women with Asherman's syndrome (intrauterine adhesions) who presented with a history of infertility or recurrent pregnancy loss were initially included in the study.

Investigations

Before treatment, all of the patients underwent preoperative evaluations, including pelvic ultrasonography, biphasic basal body temperature chart, tubal patency test, and spouse's semen analysis. Serum hormone measurements (E₂, P, androgens, LH, FSH, and PRL) were evaluated on the fifth day of the menstrual cycle or at a randomly chosen time in patients who had amenorrhea. Any patients with other significant causes of reproductive failure, such as grossly abnormal semen analysis, ovarian failure (FSH >40 U/L), or bilateral

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blocked tubes (after hysteroscopic surgery), were excluded from the data. Nine cases of endometrial tuberculosis diagnosed by endometrial histology were also excluded.

There were 36 cases in which tubal patency could not be confirmed before hysteroscopic surgery. In these 36 cases, concurrent laparoscopy was carried out at the time of hysteroscopic adhesiolysis. Among them, 32 cases had patent tubes and 4 had bilateral blocked tubes; the latter were therefore excluded from further analysis. In total, 85 cases were included in the final analysis.

Classification

All cases were diagnosed hysteroscopically and classified according to a modified classification based on the European Society of Hysteroscopy (ESH) and European Society of Gynaecological Endoscopy (ESGE) classification of Intrauterine adhesions (1995 version) (10). The modified classification and extent of the 85 cases in the final analysis are summarized in Table 1.

Procedure

The adhesions were divided or transected hysteroscopically by three experienced surgeons in our unit with the use of similar techniques, using electrode needle or loop under direct vision. The cutting and coagulating power was set at 80 W and 60 W, respectively. Five-percent glucose or mannitol

was used as a distension medium. In cases of adhesions in the cervical canal, Hegar's dilators were used to sound and dilate the cervical canal under ultrasound guidance. Afterward, hysteroscopic lysis of adhesions was performed. In most cases, the filmy and central adhesions were divided first, then marginal and dense adhesions were divided. The trans-abdominal ultrasonography guided the hysteroscopy toward the uterine cavity even though the adhesions may have obliterated the uterine cavity. The occurrence of any complications was recorded.

At the end of the procedure, a T-shaped intrauterine contraceptive device (IUCD) was inserted into the uterine cavity and hormone treatment was started, consisting of estradiol valerate at a dose of 4 mg/day for 22 days, with the addition of medroxyprogesterone acetate at a dose of 10 mg/day in the last ten days of the estrogen treatment. Thereafter, if the patient had a withdrawal bleed, cyclical hormone treatment was repeated for a further 2 months with a break between the treatment cycles. After 3 months, a second look hysteroscopy was performed in the early proliferative phase of the menstrual cycle in those patients who were menstruating. In the 11 patients who remained amenorrhoeic, hysteroscopy was performed at a randomly chosen time. If reformation of adhesions had occurred, a repeat adhesiolysis procedure was performed during the second look procedure. The IUCD was removed during the second

TABLE 1

Modified classification based on European Society of Gynaecological Endoscopy (ESGE) classification of 85 patients with Asherman's syndrome.

Modified grade	ESGE grade	Extent of intrauterine adhesions	Cases of infertility	Cases of recurrent miscarriage	Total
Mild	I	Thin or filmy adhesions	16	1	17 (22.7%)
	II	Singular dense adhesion			
Moderate Severe	IIa	Occluding adhesions only in the region of the internal cervical os	20	8	28 (32.9%)
	III	Multiple dense adhesions			
	IV	Extensive dense adhesions with (partial) occlusion of the uterine cavity			
	Va	Extensive endometrial scarring and fibrosis in combination with grade I or grade II adhesions	36	4	40 (47.1%)
	Vb	Extensive endometrial scarring and fibrosis			
Total			72	13	85

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look hysteroscopy after the presence or absence of adhesion was observed. If a repeat adhesiolysis procedure was performed, a second IUCD was inserted into the uterine cavity and hormone treatment was started again. In cases of absence of adhesion at second look hysteroscopy, no further surgery was required. Thereafter, the patients would resume their efforts to conceive and were contacted routinely at 6 month intervals for a year, and then annually. The menstrual pattern, the time interval to conceive, and the reproductive outcome were recorded.

The results are presented as mean \pm SD for quantitative variables and frequency (percentage) for qualitative variables.

RESULTS

Patient Characteristics

The age of the 85 patients included in the final analysis ranged from 22 years to 43 years (mean 31.1 years). Among them, six patients (7.1%) had a history of curettage on postpartum uterine cavity; 13 patients (15.3%) had a history of curettage for miscarriages; 36 patients (42.4%) had a history of terminations of pregnancies; five patients (5.9%) had a history of curettage on nongravid uterus; 4 patients (4.7%) had a history of hysteroscopic surgery, including polypectomy ($n = 1$), myomectomy ($n = 2$), and resection of septum ($n = 1$); one patient (1.2%) had transabdominal resection of septum before; and the remaining 20 patients (23.5%) had no obvious explanation for the occurrence of intrauterine adhesions.

Among the 85 cases, 72 women had a history of infertility for more than one year, including primary infertility in 14 cases and secondary infertility in 58 cases; 13 women had recurrent pregnancy loss (≥ 3 spontaneous miscarriages). Sixty-two of the women had reduced menstrual flow, with amenorrhea in 33 cases and hypomenorrhea in 29 cases. Among the 62 women with reduced menstrual flow, 15 women experienced cyclic pelvic pain.

The duration of follow-up for the 85 patients ranged from 1 year to 8 years, with a mean (\pm SD) of 3.9 ± 0.6 years.

A total of 109 procedures of adhesiolysis were performed in the 85 patients: 64 women had one procedure, 19 women had two procedures, and 2 women had more than two procedures. Operative complications included a uterine perforation in one patient (0.9%) with severe adhesions and false channel in three (2.8%), including one case with adhesion in the cervical canal and two cases with severe intrauterine adhesions. All of the complications were recognized at the time of intrauterine dissection and none of them required specific treatment. Sixty-one patients had second look hysteroscopy performed 3 months after the initial hysteroscopic adhesiolysis in our unit. Among them, 22 patients had third or fourth look hysteroscopy after further adhesiolysis. Fourteen patients had second look hysteroscopy performed in local hospitals. Ten patients failed to have second look hysteroscopy.

Menstrual Pattern After Surgery

After the hysteroscopic surgery, 11 women were amenorrhoeic, 23 women had hypomenorrhoea, and 51 women experienced normal menstruation. The preoperative menstrual abnormalities were improved in 46 patients (46 out of 62; 74.2%). Paradoxically, four cases (4.7%) presented with reduced menstrual flow after treatment. One patient with hypomenorrhea preoperatively had amenorrhea after treatment, and three patients with normal menses preoperatively presented with hypomenorrhea after treatment.

The proportions of women with amenorrhea, hypomenorrhea, and normal periods before and after surgery were 33/29/23 and 11/23/51, respectively. The correlation between conception and menstrual pattern before and after hysteroscopic adhesiolysis is listed in Table 2. Two-by-three contingency table analysis suggested no significant association ($P > .05$) between conception rate after treatment and the preoperative menstrual pattern. However, a significant association ($P < .05$) was found between conception and menstrual pattern after treatment. In women who had amenorrhea after treatment, only two conceptions occurred. The first woman who failed to have second look hysteroscopy conceived 10 months after adhesiolysis. The other woman who had a normal uterine cavity at second look hysteroscopy conceived 14 months after treatment. Therefore, the likelihood of conception (2 out of 11; 18.2%) in women who had amenorrhea after treatment was significantly lower ($P < .05$) than those who continued to have periods (37 out of 74; 50%).

Second Look Hysteroscopy

At second look hysteroscopy ($n = 61$), there was no reformation of adhesions in women who previously had mild adhesions. The rates of reformation of adhesions in women with moderate and severe adhesions were 16.7% (4 out of 24) and 41.9% (13 out of 31) respectively. The relationship between the severity of adhesions before and after hysteroscopic surgery and further analysis of conception according to the severity of adhesions at second look hysteroscopy is shown in Table 3. Two-by-two contingency table analysis showed that the conception rate in women who had reformation of intrauterine adhesions at second look hysteroscopy (2 out of 17; 11.8%) was significantly lower than that of women who had a normal cavity (26 out of 44; 59.1%; $P < .05$). No conceptions occurred in the severe recurrence group.

Conception and Reproductive Outcome

Among 85 women, 39 (45.9%) achieved pregnancy. Among 72 women who had a history of infertility, four had IVF treatment after the procedures but none of them conceived. None of the women (0/4) who were 40 to 43 years old at the time of treatment conceived after surgery. Of 39 pregnancies, 25 (64.1%) achieved a live birth, eight (20.5%) had spontaneous miscarriage, and five (12.8%) had an ongoing pregnancy (three pregnancies were less than 12 weeks and two

TABLE 2**Menstrual pattern before and after hysteroscopic adhesiolysis and relationship to conception rate.**

Menstrual pattern before treatment (n = 85)	Menstrual patterns after treatment			
	Amenorrhea (n = 11)	Hypomenorrhea (n = 23)	Normal menses (n = 51)	Conception rate (%)
Amenorrhea (n = 33)	2/10	4/15	7/8	13/33 (39.4%)
Hypomenorrhea (n = 29)	0/1	3/5	11/23	14/29 (48.3%)
Normal menses (n = 23)	0	1/3	11/20	12/23 (52.2%)
Conception rate (%)	2/11 (18.2%)	8/23 (34.8%)	29/51 (56.9%)	39/85 (45.9%)

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pregnancies were more than 12 weeks at the time of final follow-up). One pregnancy was terminated at 7 weeks gestation at the patient's request. Among the 25 women who had a live birth, five had abnormal placenta. Two women who had had severe adhesions at the first hysteroscopy had hysterectomies after delivery because of placental accrete and uncontrolled hemorrhage. Three women who had moderate intrauterine adhesions at the first hysteroscopy required manual removal of placenta after delivery for placental adherence. Two women who delivered at 26–28 pregnancy weeks had low-birth-weight babies, but there was no evidence of significant intrauterine growth restriction in the babies delivered in this study. Among women with a history of infertility (n = 72), 31 conceptions (43.1%) occurred. The outcomes of those 31 conceptions are summarized in Table 4A. Among women

with a history of recurrent pregnancy loss (n = 13), eight conceptions (61.5%) occurred. The outcomes of those eight conceptions were summarized in Table 4B.

Cumulative Conception Rate

The cumulative conception rates (CCR) for the subjects who conceived were calculated as 1 – survival rate, which was based on Kaplan-Meier survival rates and are shown in Figure 1. In total, 87.2% (34 out of 39) of all pregnancies occurred within 2 years after removal of the IUCD.

Factors Affecting Conceptions

The various factors which may affect conception rate after hysteroscopic adhesiolysis were analyzed:

TABLE 3**Reformation of intrauterine adhesions confirmed by second look hysteroscopy and relationship to conception rate.**

Severity	Before treatment		After treatment (second look)			Recurrence of adhesion
	Number of cases	Normal cavity	Mild	Moderate	Severe	
Mild	6	6	0	0	0	0
Moderate	24	20	0	3	1	4/24 (16.7%)
Severe	31	18	1	8	4	13/31 (41.9%)
Total	61	44	1	11	5	17/61 (27.9%)
Conception rate (%)		26/44 (59.1%)		2/17 (11.8%)		28/61 (45.9%) ^a

^a Conception rate in 61 women who had second look hysteroscopy.

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TABLE 4

Reproductive outcome after hysteroscopic treatment of Asherman's syndrome.

Number of cases	Pregnancy	Spontaneous miscarriage ^a	Ongoing ^a	Preterm delivery ^a	Term delivery ^a	Live birth ^a
A. Patients with a history of infertility (n = 72)						
Mild	10/16 (62.5%)	2/10 (20%)	1/10 (10%)	1/10 (10%)	6/10 (60%)	7/10 (70%)
Moderate	9/20 (45%)	2/9 (22.2%)	1/9 (11.1%)	2/9 (22.2%)	4/9 (44.4%)	6/9 (66.7%)
Severe	12 ^b /36 (33.3%)	3/12 (25.0%)	2/12 (16.7%)	2/12 (16.7%)	4/12 (33.3%)	6/12 (50%)
Total	31/72 (43.1%)	7/31 (22.6%)	4/31 (12.9%)	5/31 (16.1%)	14/31 (45.2%)	19/31 (61.3%)
B. Patients with a history of recurrent (≥3) pregnancy loss (n = 13)						
Mild	1/1 (100%)	0	0	1/1 (100%)	0	1/1 (100%)
Moderate	6/8 (75%)	1/6 (16.7%)	1/6 (16.7%)	1/6 (16.7%)	3/6 (50%)	4/6 (66.7%)
Severe	1/4 (25%)	0	0	0	1/1 (100%)	1/1 (100%)
Total	8/13 (61.5%)	1/8 (12.5%)	1/8 (12.5%)	2/8 (25%)	4/8 (50%)	6/8 (75%)

^a Per pregnancy.

^b Including one pregnancy terminated at 7 weeks at patient's request.

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1. Menstrual pattern before surgery: The conception rates in women with amenorrhea, hypomenorrhea, and normal period before surgery were 39.4%, 48.3%, and 52.2%, respectively (Table 2; three-by-two contingency table analysis; $P>.05$).
2. Menstrual pattern after surgery: The conception rate in women with amenorrhea, hypomenorrhea, and normal period after surgery were 18.2%, 34.8%, and 56.9%, respectively (Table 2; three-by-two contingency table analysis; $P<.05$).
3. Severity of adhesions before surgery: The conception rate in women with mild, moderate, and severe adhesions before surgery were 64.7% (11 out of 17), 53.6% (15 out of 28), and 32.5% (13 out of 40), respectively (three-by-two contingency table analysis; $P=.05$).
4. Reformation of adhesions after surgery: Among 17 cases with reformation of intrauterine adhesions at second look hysteroscopy, only two conceptions (11.8%) occurred despite further adhesiolysis. Among 44 women with normal cavities at second look hysteroscopy, 26 conceptions (59.1%) occurred (Table 3; two-by-two contingency table analysis; $P<.05$).

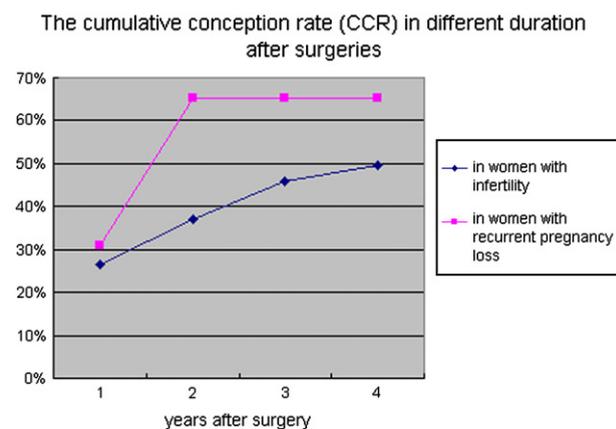
DISCUSSION

Classification of Disease and Selection of Cases

In the present study, we have reported on the outcome of a consecutive series of 85 cases of hysteroscopic adhesiolysis for Asherman's syndrome. Although there have been a number of reports on the subject in the literature, it is difficult to directly compare the results for several reasons. First, the classification of the severity of the intrauterine adhesions is not uniform even though it is well recognized that the

FIGURE 1

Cumulative conception rates (CCR) after hysteroscopic adhesiolysis in women with Asherman's syndrome.



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outcome of treatment depends on the severity of the disease (1, 7, 11, 12). Second, very few authors presented the results of treatment according to the presenting symptoms (1, 6). Some women with Asherman's syndrome present with hypo- or amenorrhea, some with infertility, and others with recurrent pregnancy loss. It is quite possible that the presenting symptom may affect the outcome. Third, the reproductive outcomes in many earlier reports were simply presented as crude pregnancy rate (1, 2, 6, 11, 12) without reference to the duration of follow-up and the cumulative conception rate, which is a much more refined method of presenting data on conception after treatment.

In the present study, we have attempted to address the above concerns. First, we have classified the severity of the syndrome according to ESGE classification of intrauterine adhesions (1995 version). Second, we have examined the reproductive outcome of women who presented only with reproductive failure, either infertility or recurrent pregnancy loss. We have not included women who simply presented with hypomenorrhea or amenorrhea, because it is likely that the reproductive outcomes in this group of subjects differ from those who experienced infertility or recurrent pregnancy loss. Furthermore, we have further subdivided subjects with a view to establishing whether or not these two groups of subjects (infertility and pregnancy loss) differ in the outcomes. Third, in the study of women with infertility, we have excluded couples with additional infertility factors, because they would undoubtedly affect the outcome. Finally, we have presented not only data on the crude conception rate but also data on the duration of follow-up and the cumulative conception rate.

Menstrual Pattern and Conception Rate

It has been reported that the return of menstruation after hysteroscopic treatment ranges from 52.4% (11 out of 21) to 88.2% (149 out of 169) (1, 8, 13). In the present data, the improvement of menstrual flow was 74.2% (46 out of 62), which was similar to earlier reports. In addition, we found that the menstrual pattern before hysteroscopic surgery did not appear to have a significant prognostic impact on conception rate, although there is trend toward a lower conception rate in women with amenorrhea and toward a higher conception rate in women with normal periods. In contrast, the menstrual pattern after hysteroscopic surgery appeared to have a significant impact ($P < .05$) on prognosis, with conception rate of 18.2% (2 out of 11) in women with amenorrhea, 34.8% (8 out of 23) in women with hypomenorrhea, and 56.9% (29 out of 51) in women with normal periods. These findings are not surprising, because it is the endometrial function (as reflected by menstrual pattern) after surgery which is important in determining the outcome.

Reformation of Adhesions

It was well known that intrauterine adhesions have a high rate of reformation after adhesiolysis (3.1%–23.5%)

(1, 4, 8), especially in severe cases (20%–62.5%) (1, 4, 7, 8). Various methods have been used to prevent the reformation of intrauterine adhesions, such as IUCD (14–17), Foley balloon catheter (18, 19), Hyaluronic acid (20), and hormone treatment (21). The insertion of an IUCD has been advocated by many authors as an effective and widely used method to prevent adhesions reformation (14–17). Farhi et al. (21) found that estrogen-progestin therapy significantly increases endometrial thickness and volume. Therefore, we routinely used IUCD and cyclical hormone treatment at the end of the adhesiolysis procedure.

Most studies used hysterosalpingography to recheck the cavity, which is not a reliable method to detect intrauterine adhesions. It has been reported that the sensitivity of hysterosalpingography in the detection of intrauterine adhesions is between 75% and 79%, whereas the positive predictive value is as low as 43% (22, 23). In the present study, we used second look diagnostic hysteroscopy to check the uterine cavity 3 months after surgery. Hysteroscopy, as compared with other radiologic tests, can more accurately confirm the presence, extent, and degree of adhesions and the quality of the endometrium, because the uterine cavity can be directly inspected. This method has been considered to be the golden standard for investigation of intrauterine adhesions.

Among 61 cases of second look hysteroscopy, the overall rate of recurrent adhesion was 27.9% (17 out of 61). In severe cases, the rate of recurrent adhesions was 41.9% (13 out of 31). Among 17 cases with reformation of intrauterine adhesions at second look hysteroscopy, only two conceptions (11.8%) occurred despite further adhesiolysis. Among 44 women with normal cavities at second look hysteroscopy, 26 conceptions occurred (59.1%; two-by-two contingency table analysis; $P < .05$). Therefore, we conclude that the reformation of adhesions had a significant impact on the conception rate after hysteroscopic adhesiolysis.

Severity of Intrauterine Adhesions Before Surgery and Conception Rate

In the present study, we observed that the severity of intrauterine adhesions before hysteroscopic adhesiolysis appeared to affect the conception rate after hysteroscopic adhesiolysis. The conception rate in women with mild, moderate, and severe adhesions were 64.7%, 53.6%, and 32.5% respectively. The difference observed was of borderline statistical significance ($P = .05$).

Worsened Outcome After Surgery

It is assumed that hysteroscopic adhesiolysis would improve clinical outcome, but that may not always be the case. It seems that in a small proportion of cases, around 5% (4 out of 85) in the present series, the menstrual flow decreased after hysteroscopic surgery. It is of interest to note that at the

second look hysteroscopy, although 53 out of 61 cases (86.9%) had a better outcome (normal or reduced adhesions), seven cases (11.5%) had findings the same as before surgery and one case (1.6%) had a worse outcome than before surgery, i.e., more severe adhesions than what was present before the surgical intervention. It is possible that reformation of adhesions contributed to the worsened outcome.

Miscarriage, Preterm Delivery, and Live Birth Rate

In the present series, the overall conception rate after hysteroscopic surgery was 45.9%, which was similar to those reported by Roge et al. (2) (28 conceptions out of 52 patients after adhesiolysis; 54%). In the present series, among those who managed to conceive, the live birth rate was 64.1%, which was again similar to several earlier reports (71%–79%) (1, 4). The live birth rate of 64% is slightly lower than that expected of the average population, partly because of the slightly higher miscarriage rate (20.5%) and partly because we have not included ongoing pregnancy in the calculation.

It is of interest to note that the preterm delivery rate in our series was 17.9%. Others have reported preterm delivery rates of 25%–50% (2, 9). These rates suggest that pregnancies after hysteroscopic adhesiolysis for Asherman's syndrome should be considered as high risk for preterm delivery and should be monitored carefully in the second and third trimesters.

Secondary Look and Conception Interval

In the analysis of CCR between second look and conception intervals, 23 conceptions (23 out of 39; 59.0%) occurred within 1 year after treatment and 34 conceptions (34 out of 39; 87.2%) occurred within 2 years after treatment. It is interesting to note that the CCR for women who presented with infertility and recurrent pregnancy loss are rather different, in that the CCR for women with recurrent miscarriage plateaued very quickly at year 2, whereas the CCR for women who presented with infertility rose gradually and continued to go up by year 4.

Factors Affecting Conception

From the analysis of the present data, two factors significantly influenced the conception rate after hysteroscopic adhesiolysis: menstrual pattern after treatment and reformation of intrauterine adhesions. The severity of intrauterine adhesions, which was of borderline statistical significance, may also influence the prognosis.

Conclusion

In this study, we have analyzed the reproductive outcome of hysteroscopic adhesiolysis in women with Asherman's syndrome presenting with either infertility or recurrent miscarriage. The overall conception after treatment was 45.9% (39 out of 85). Women who experienced normal periods after the procedure and women who had a normal uterine cavity at

second look hysteroscopy were significantly more likely to conceive than those who continued to experience hypo/amenorrhea and who developed recurrence of adhesions. Further research in Asherman's syndrome should be directed toward reduction of adhesion reformation with a view to improving outcome.

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