

Reproductive Outcome of Patients with Asherman's Syndrome: A SAIMS Experience

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Abstract

Background: The purpose of the study was to evaluate menstrual and reproductive outcome in patients diagnosed with Asherman's syndrome on hysteroscopy and to assess the role of hysteroscopic adhesiolysis.

Methods: A prospective study was performed for patients having intrauterine adhesion at a tertiary care teaching hospital, Indore, India for a period of 2 years. Findings at hysteroscopy, details of adhesiolysis, changes in menstrual pattern following adhesiolysis, need for repeat procedure and fertility outcome were prospectively collected. Data was analysed using SPSS software. A p-value of <0.05 was considered significant.

Results: A total of 60 patients with a mean age of 30.1 ± 5.5 years with Asherman's syndrome were included. In 53.3% of them, no factors like post-partum curettage, uterine surgery or history of tuberculosis could be found in which the present intrauterine adhesions could be attributed to. Hypomenorrhoea was the most common (53.3%) menstrual pattern in patients diagnosed with Asherman's syndrome. Thirty eight out of 60 (63.33%) required second look hysteroscopy. There was a significant change in endometrial lining and echo pattern after adhesiolysis ($p < 0.05$). 45% of patients started having normal menstrual flow after adhesiolysis which was statistically significant. A total of 16 conceptions and 10 live births were reported in the present cohort. Pregnancy rate was higher in patients having mild Asherman's syndrome (53.3%) as compared to moderate (26.9%) or severe type (9.5%), ($p = 0.0049$). It was also higher in patients having normal endometrial pattern after adhesiolysis ($p = 0.0005$).

Conclusion: Women who underwent hysteroscopic adhesiolysis showed significant improvement in the menstrual pattern. Pregnancy rates were improved after hysteroscopic adhesiolysis.

Keywords: Adhesiolysis, Asherman's syndrome, Hysteroscopy, Menstrual pattern, Pregnancy.

To cite this article: Bhandari Sh, Bhawe P, Ganguly I, Baxi A, Agarwal P. Reproductive Outcome of Patients with Asherman's Syndrome: A SAIMS Experience. J Reprod Infertil. 2015;16(4):229-235.

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Received: Dec. 15, 2014

Accepted: Apr. 19, 2015

Introduction

Joseph Asherman defined Asherman's syndrome in 1948 as a case of severe intrauterine adhesions secondary to trauma to gravid uterus. Specifically, he identified this pathology in 29 women who showed amenorrhea with stenosis of internal cervical os (1). Pregnant uterus is more susceptible to develop scarring but any trauma even in non pregnant state to the endome-

trium can cause intrauterine adhesions. Today, this terminology encompasses all cases of intrauterine permanent adhesions which obliterate, partially or completely, the uterine cavity, irrespective of the cause. Other than trauma to gravid uterus, the etiological factors leading to Asherman's syndrome are mullerian duct malformation, genital tuberculosis, insertion of intrauterine de-

vice and uterine surgery like caesarian section, diagnostic curettage, myomectomy, hysteroscopy surgery, *etc.* (2).

The patients of intrauterine adhesions (IUA) generally present with amenorrhea or other menstrual aberrations, recurrent pregnancy loss and infertility. It is also important to underline that there are many cases reported in the literature where presence of interauterine adhesions is not associated with any symptoms (3). Pregnancy after IUAs may be complicated by abortion, premature labor, placenta previa and placenta accreta (4, 5).

During the last two decades, the advent of hysteroscopy has revolutionized the diagnosis and management of Asherman's syndrome. Historically, the use of hysterosalpingography (HSG) has been widespread in the diagnosis but hysteroscopy is now the gold standard of diagnosis and treatment of Asherman's syndrome (2).

Asherman's syndrome is a condition with a high impact on female reproduction. In the past, many studies have been performed to evaluate reproductive outcome in cases of Asherman's syndrome (4-7). In previous report by Yu et al., (5) hysteroscopic adhesiolysis achieved successful anatomical restoration in 57.8% to 97.5% of cases. They reported adhesion reformation (3.1 to 23.5%) to be the major limiting step to success of the treatment which warranted repeat procedures.

However, there is scanty data in Indian scenario regarding Asherman's syndrome and its type of presentation, severity of adhesions, recurrence and impact on menstrual pattern (8-10). The nature of disease presentation in Indian subcontinent is distinguished by different incidence of etiological factors especially genital tuberculosis. Studies have shown that genital tuberculosis seems to be associated with recurrence of IUA and poor prognosis after hysteroscopic surgery (11).

The present study aimed to analyze the outcome of hysteroscopic adhesiolysis in 60 women with Asherman's syndrome by observing the stage of disease, re-establishment of cavity, post-operative menstrual pattern and pregnancy rates.

Methods

The study was conducted in the Department of Reproductive Medicine, Sri Aurobindo Institute of Medical Sciences, India. Patients reporting to the Department of Reproductive Medicine for infertility were evaluated as per departmental protocol which included detailed history, semen analysis,

baseline transvaginal ultrasound, routine blood investigations (including serum TSH, prolactin, FSH). Patients with male factor infertility, ovulatory factors or any other uterine malformation like fibroid uterus were excluded from the study. Patients diagnosed with intrauterine adhesions and no other demonstrable causes of infertility were considered in the study.

From January 2012 to December 2013, 85 patients were diagnosed with intrauterine adhesions by hysteroscopy done with or without concurrent laparoscopy. Out of these, 3 patients had elevated serum FSH and 22 patients were lost to follow up. Therefore, a total of 60 patients were included in the study for further analysis. Intrauterine adhesions diagnosed on hysteroscopy were classified according to modified classification based on European Society of Gynecological Endoscopy (ESGE) (10). Patient details including age, past conception, duration of infertility, past menstrual cycles, findings of ultrasonography (including premenstrual endometrial thickness) and findings of hysterosalpingography were recorded.

To analyze the causative factors of Asherman's syndrome, history of curettage (post-partum or for miscarriage) and any uterine surgery was recorded. Patients with history of genital or extra genital tuberculosis diagnosed by acid fast bacilli (AFB) culture and/or histopathology were considered as having positive history for tuberculosis. At the time of hysteroscopy, endometrial biopsy was taken using Novak's curette (whenever possible) and real time polymerase chain reaction (RT-PCR) for tuberculosis was performed in patients who had not taken antitubercular therapy in the past. AFB culture was also performed in few selected cases where clinical suspicion of tuberculosis was high.

Hysteroscopic adhesiolysis was performed for all patients by a single operator (SB) using hysteroscopic scissors (Karl Storz, Germany). Concurrent laparoscopy was done in patients where tubal factor infertility was also suspected or wherein hysteroscopy required laparoscopic guidance. In some cases, transabdominal B-mode ultrasound was also used to guide the procedure. Absence of filling of tube or absence of spill from fimbria was considered cornual and fimbrial block, respectively. Tubes showing dilatation, sacculations or multiple constrictions along the length with agglutinated fimbria were considered to have multiple tubal blocks.

Adhesiolysis began inferiorly and proceeded towards fundus until a panoramic view of the cavity was obtained and the ostia were visualized. In severe cases, the procedure was discontinued when pink myometrium was seen, even if ostia were not visualized. The occurrence of any intra or postoperative complications was recorded.

Postoperatively, all patients were given estradiol valerate up to 8 mg per day in divided doses for no more than 28 days and ultrasonography (USG) was done to check changes in endometrial thickness.

Patients who did not show any improvement in their menstrual flow and/ or endometrial echoes in USG were subjected to second or third hysteroscopy. No patient was subjected to more than 3 procedures.

Patients were followed up every 3 months for a period of 6 months to 2 years. Details of changes in menstrual flow, spontaneous conception and reproductive outcome were recorded. *In vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) was done in patients who had associated causes like tubal factor infertility or were unable to conceive spontaneously during 1 year.

Patients were counseled regarding the study and detailed consent was taken before their inclusion in the cohort and approval from institutional ethics committee was taken before the study.

Statistical analysis was done using SPSS software 20.0. Mc-Nemar and Pearson chi square test was performed for paired and unpaired samples, respectively to see the difference in frequencies of endometrial echo pattern and menstrual pattern in pre-operative and post-operative patients as well as to see the difference in pregnancy rates in the two groups. A $p < 0.05$ was considered significant.

Results

The mean age of the patients was 30.1 ± 5.5 years (range 23 to 41 years) and mean duration of infertility was 9.2 ± 6.4 years. Among the 60 patients, 58 presented with infertility (44 primary and 14 secondary) whereas 2 patients had history of recurrent pregnancy loss. The most common menstrual pattern amongst these patients was hypomenorrhoea (Table 1).

Among the various etiological factors evaluated, in 53.3% of patients, no obvious cause for Asherman's syndrome was found. History of tuberculosis was the main cause for Asherman's syndrome

Table 1. Demographic profile of the patients

| Variables | Number (%) |
|--|------------|
| Primary infertility | 44(73.3) |
| Secondary infertility | 14(23.3) |
| Recurrent pregnancy loss | 2(3.3) |
| Causes of Asherman's syndrome | |
| H/O tuberculosis | 8(13.3) |
| H/O post-partum curettage | 2(3.3) |
| H/O abortion (D&C) | 4(6.7) |
| H/O diagnostic curettage | 6(10.0) |
| H/O myomectomy | 1(1.6) |
| H/O hysteroscopic surgery | 0(0) |
| H/O uterine surgery/procedure | 1(1.6) |
| No significant causative factor in patients' history | 32(53.3) |
| H/O LSCS | 4(6.7) |
| Associated tubal factor infertility | 35(58.3) |
| Menstrual pattern | |
| Hypomenorrhoea | 32(53.3) |
| Amenorrhoea | 16(26.7) |
| Normal periods | 12(20.0) |

H/O=History of, D&C=Dilatation and curettage, LSCS=Lower Segment Cesarean Section

Table 2. Findings of hysteroscopy at different sittings

| | First | Second | Third |
|----------|----------|----------|---------|
| Normal | | 6(15.7) | 1(16.7) |
| Mild | 13(21.7) | 8(21.0) | 0(0) |
| Moderate | 26(43.3) | 15(39.4) | 3(50.0) |
| Severe | 21(35.0) | 8(21.0) | 2(33.3) |
| Total | 60(100) | 38(100) | 6(100) |

Number in parenthesis represents percentage

(13.3%) followed by history of diagnostic curettage (Table 1).

26 (43.3%) patients of Asherman's syndrome had moderate adhesions in the first hysteroscopic procedure (Table 2). Out of 60, 38 (63.3%) patients underwent second hysteroscopy after 2 months as they did not show any improvement in their endometrial echoes in ultrasonography or menstrual flow. Out of these 38 patients, 6 did not have any adhesions and had restoration of volume and size of the cavity. Six patients underwent third hysteroscopy of which 5 had persistently moderate to severe adhesions. Of the 21 patients with severe adhesions at first sitting, 2 had persistently severe adhesions even after third hysteroscopic adhesiolysis. Endometrial gland openings were not noted or identified in the epithelial lining of any of these patients.

Table 3. Endometrial pattern in relation to menstrual pattern

| Preoperative menstrual pattern | Preoperative endometrial pattern | | | | |
|--------------------------------|----------------------------------|----------|-----------|---------|----------|
| | Normal | Thin | Irregular | Fluid | Total |
| Amenorrhea | 0(0) | 9(25.7) | 4(40) | 3(25) | 16(26.7) |
| Hypomenorrhea | 0(0) | 21(60.0) | 6(60) | 5(41.7) | 32(53.3) |
| Normal | 3(100) | 5(14.3) | 0 | 4(33.3) | 12(20) |
| Total | 3(100) | 35(100) | 10(100) | 12(100) | 60 |

Number in parenthesis represents percentage

Concomitant laparoscopy was performed in 42 patients whenever required. In 3 patients, there were no pelvic or abdominal adhesions whereas out of 39 (92.2%) patients in which positive findings were seen by laparoscopy, multiple tubal blocks was the most common finding (16, 38.1%) followed by fimbrial block (9, 21.4%). Other findings include cornual block (6, 14.3%), frozen pelvis (3, 7.1%) and abdominal adhesions (3, 7.1%) including perihepatic adhesions in 1 patient.

Endometrial biopsy could be performed in 47 patients as tissue was insufficient in rest of the cases. It showed tuberculous endometritis in 13 cases. Positive PCR on endometrial aspirate was seen in 15/34 women. All patients underwent pre-operative transvaginal USG in the premenstrual phase or at a random phase in patients with amenorrhea to evaluate uterine cavity and endometrial pattern (Table 3).

Thin endometrial echoes were the most common findings on transvaginal ultrasound prior to adhesiolysis and out of these 35 thin endometrial echoes 21(60.0%) patients had hypomenorrhoea (Table 4). A significant association of type of echoes with their menstrual pattern was observed as well ($p=0.009$).

Even after one or more attempts at adhesiolysis, thin endometrium remained the most common finding. Post-operative normal echo pattern had maximum development in patients who had fluid in uterine cavity, preoperatively (Table 4). There was a significant change in endometrial echo after adhesiolysis ($p<0.0001$). The patients who continued to have thin endometrium had moderate to severe adhesions on hysteroscopy.

Nine patients had postoperative amenorrhea and out of these 9 patients, 7 patients had severe type of Asherman's syndrome. All patients with mild Asherman's syndrome had normal menstrual pattern postoperatively.

After adhesiolysis, 27 out of 60 patients (45%) had normal menstrual pattern. Out of 32 patients

Table 4. Pre and postoperative endometrial echoes

| Postoperative endometrial echoes | Preoperative endometrial echoes | | | | |
|----------------------------------|---------------------------------|----------|-----------|---------|----------|
| | Normal | Thin | Irregular | Fluid | Total |
| Normal | 2(66.7) | 13(37.1) | 0(0) | 7(58.4) | 22(36.7) |
| Thin | 1(33.3) | 19(54.3) | 7(70) | 1(8.3) | 28(46.7) |
| Irregular | 0(0) | 1(2.9) | 3(30) | 0(0) | 4(6.6) |
| Fluid | 0(0) | 2(5.7) | 0(0) | 4(33.3) | 6(10.0) |
| Total | 3(100) | 35(100) | 10(100) | 12(100) | 60(100) |

Number in parenthesis represents percentage

Table 5. Pre and postoperative menstrual pattern

| Before treatment | Menstrual patterns after treatment | | |
|----------------------|------------------------------------|---------------|----------|
| | Amenorrhea | Hypomenorrhea | Normal |
| Amenorrhea [n=16] | 6(37.5) | 10(62.5) | 0(0) |
| Hypomenorrhea [n=32] | 3(9.3) | 13(40.6) | 16(50.0) |
| Normal menses [n=12] | 0(0) | 1(8.3) | 11(91.7) |
| Total [n=60] | 9(15.0) | 24(40.0) | 27(45.0) |

Number in parenthesis represents percentage

of preoperative hypomenorrhea, 16 had normally developed menstrual pattern while menstrual flow was attained in 10 out 16 preoperative amenorrhea patients (Table 5). Paradoxically, 1 patient who had previous normal menstrual cycle developed hypomenorrhea after adhesiolysis.

After adhesiolysis, four patients conceived spontaneously within 2 years of treatment. Assisted reproductive technology (IVF/ICSI) could be applied in only 23 patients as others did not give their consent. Controlled ovarian stimulation was done using antagonist protocol in all patients. An average of 15.4 oocytes were retrieved per stimulation cycle. IVF/ICSI done resulted in an average of 9.6 embryos per patient. An average of 3-5 embryos was transferred depending on the patient's age, endometrial pattern and embryo quality. Remaining embryos were cryopreserved. Twelve patients conceived after 1 or more embryo transfers. Five patients conceived after first embryo transfer while 7 conceived after repeat frozen thaw cycles.

Table 6. Reproductive profile according to severity and treatment outcome

| | Total | Pregnancy | Miscarriage | Preterm | Live birth | Ongoing |
|--|-------|-----------|-------------|---------|------------|---------|
| Degree of severity | | | | | | |
| Mild | 13 | 7(53.8) | 1(7.7) | 1(7.7) | 5(38.5) | 1(7.7) |
| Moderate | 26 | 7(26.9) | 2(7.7) | 0(0.0) | 4(15.4) | 1(3.8) |
| Severe | 21 | 2(9.5) | 0(0.0) | 1(4.8) | 1(4.8) | 0(0.0) |
| Post treatment endometrial echoes | | | | | | |
| Normal | 22 | 12(54.5) | 2(9.1) | 1(4.6) | 9(40.9) | 1(4.6) |
| Altered | 38 | 4(10.5) | 1(2.6) | 1(2.6) | 1(2.6) | 1(2.6) |
| Post treatment menstrual pattern | | | | | | |
| Normal | 27 | 9(33.3) | 1(3.7) | 1(3.7) | 7(25.9) | 1(3.7) |
| Altered | 33 | 7(21.2) | 2(6.1) | 1(3.0) | 3(9.1) | 1(3.0) |

Number in parenthesis represents percentage

Implantation rate and pregnancy rate per initiated cycle were 23.8% and 52.17%, respectively.

Out of 16 patients conceived, 9 patients did not require a repeat hysteroscopic procedure. The maximum rate of conception was seen in mild type of Asherman's syndrome (53.3%).

There was a significant difference in pregnancy rate according to the severity of Asherman's syndrome (Table 6). The pregnancy rate decreased as the severity increased ($p=0.0049$).

The pregnancy rate was also dependent on post-operative endometrial pattern. A significantly higher pregnancy rate was seen in patients with normal endometrial echoes after adhesiolysis ($p=0.0005$). Pregnancy rate was higher in patients with normal postoperative menstrual flow than altered menstrual flow; however, the difference did not reach statistical significance ($p=0.382$).

Out of 16, 2 pregnancies were ongoing at the time of analysis, 10 achieved live birth, while 3 had preterm deliveries (Table 6). One preterm neonate died due to respiratory distress. One patient had post-partum hemorrhage due to retained placenta. No patient required operative interference. No case of placenta accreta was noted.

Discussion

In the present study, the reproductive and menstrual outcome of 60 cases of hysteroscopic adhesiolysis for Asherman's syndrome was reported. The demographic profile of the patients in the present study is comparable to that of other studies (4-8).

Regarding etiology, post-partum curettage has been regarded as the most common cause in previous studies (1, 2); however, in our case series post-partum curettage was seen in only 3.3% of patients. The possible reason for this discrepancy

may be due to the fact that our patient profile belongs to the region with a high prevalence of tuberculosis. This finding is comparable to studies from Indian subcontinent wherein a history of tuberculosis was found in 67.8% of women with Asherman's syndrome (8).

In our series, tubal factor was found to be associated in 39 (92.9%) patients at the time of laparoscopy. Similar to our study, Sharma et al. (8) also found 88.9 % of females who had tubal pathology during laparoscopic findings in their series of Asherman's cases.

The resumption of menses was seen in 62.5% of patients in the present study in contrast to previous reports which show that more than 85% of resumption of periods is after adhesiolysis (4, 5, 9, 11). This stark difference in our outcome, in comparison to previous studies could be explained by the degree of adhesions found in our series. Most of our patients who had secondary amenorrhoea had totally contracted uterus. Previous literature shows that intrauterine adhesions especially tubercular in origin have propensity to damage the basal layer of endometrium preventing its regeneration (12).

In patients who started having periods, though scanty, the trilaminar pattern of endometrium in luteal phase was not seen in all cases. Malhotra et al. (9) analyzed endometrial thickness and doppler flows in patients with Asherman's syndrome and found that although there was an improvement in the endometrial thickness but the vascularity did not improve. This indicates that even if the surgery provides a desired anatomical result, normal endometrial function is not guaranteed.

It is well known that intrauterine adhesions have a high rate of reformation after adhesiolysis especially in severe cases. Rate of reformation of ad-

hesions was higher in patients with originally higher scores or severe adhesions. Our figures are slightly lower than previously reported ones (4, 13). It is believed that in our case series, the severity of original intrauterine adhesions could be responsible for reduction in adequate volume cavity and therefore the second hysteroscopy documented persistence of adhesions rather than reformation.

No statistical significance was found between preoperative menstrual pattern and conception rate ($p=0.785$). However, patients having normal menstrual period, postoperatively, have higher conception rate though this did not reach clinical significance. The conception rates also decreased in women requiring repeat procedure. Similarly, Roy et al. (7) reported that the likelihood of conception was 44.3% in those who continued to have improved menstrual pattern compared to only 10% likelihood conception rate in patients who continued to have amenorrhea after treatment. These findings were also similar to other previous reports (3, 6, 7) and clearly reflect that endometrial function (as reflected by menstrual pattern) after hysteroscopic adhesiolysis is an important factor in determining the reproductive outcome.

Pregnancy rates also depended on recurrence of adhesion as in the present study, 56.2% of patients conceived only after the first sitting. In concordance with previous reports (4, 7), conception rate was lower in patients who had recurrence of adhesions. This could be explained by the fact that reformation of intrauterine adhesion and concomitant endometrial atrophy are potential problems that may limit the success of hysteroscopic adhesiolysis.

The pregnancy rate in the present study was significantly associated with severity of adhesions and postoperative endometrial echo pattern. Patients who had mild Asherman's syndrome in their initial diagnosis showed higher conception rate as did patients who developed triple line endometrial echoes after adhesiolysis. These findings are similar to previous studies reported in literature (5, 8, 9).

The pregnancy rate in properly treated cases was 52.2% (12/23) and live birth rate was 43.4% (10/23). Longer follow-up was required to determine the cumulative conception rate of the cohort. According to Zikopoulos et al. (12), an overall cumulative delivery rate of 64.7% is expected within 2 years after the operation in patients with

no additional infertility factors who attempt to conceive naturally. Their live birth rate is higher than that mentioned by others probably because of longer follow-up period. In a previous report, the cumulative conception rate varied from 59% to 61% within 1 year and 87.2% to 97% within 2 years after hysteroscopic adhesiolysis (5, 8). In our series, the pregnancy rates were lower than any other series. This may be due to the fact that our patients reflected intrauterine adhesions mostly tubercular in origin. Many researchers (13) have proved that intrauterine adhesions due to tuberculosis have poorer prognosis than those due to other causes in terms of both conception rates and recurrence rates. This is due to the fact that tuberculosis tends to cause atrophy of the basal layer of endometrium. Therefore, restoration of anatomical defect does not restore functionality of the endometrium. This is also proven by reduced blood flow in the sub-endometrial zone even when the endometrial thickness appears normal (13).

In women with Asherman's syndrome, due to tuberculosis, the reproductive outcome is poorer in comparison to those with other causes (13). The possibility of restoration of menstrual function or endometrium is limited, in spite of hysteroscopic adhesiolysis, as there is usually complete destruction of endometrium by the mycobacterial diseases.

Conclusion

Women who underwent hysteroscopic adhesiolysis showed significant improvement in the menstrual pattern and increased rates of conception as well as live birth rate per conception. Recurrence of intrauterine adhesions is an important consideration while performing adhesiolysis and adequate precautions must be taken. The use of repeat procedures and adhesion prevention strategies are needed. Also, a meta-analysis, taking into considerations all the research conducted in Indian sub-continent about this syndrome is required to achieve a better understanding of this disease.

Conflict of Interest

The authors declare that they have no conflict of interests.

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