How can surgery increase the success rate in ART?
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MANAGEMENT OF INTRAUTERINE SYNAECHIE?

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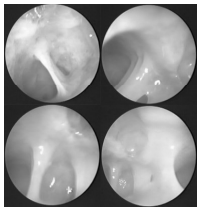
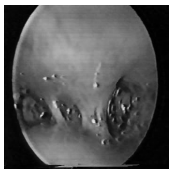
HISTORY

- ✓*1894 – Heinrich Fritsch*
  First described a case of posttraumatic intrauterine adhesion.
- ✓*1927 – Bass*
- ✓*1946 – Stamer*
- ✓*1948 – Joseph G. Asherman*
  Asherman Syndrome *has been used to describe the disease ever since.*



DEFINITION

- ✓***Intrauterine adhesions are;***
  a consequence of trauma to the endometrium, producing partial or complete obliteration in the uterine cavity and/or the cervical canal.
- ✓The prevelance varies both by different populations as well as by the types of investigation used for diagnosis. (approximately %1,5)



Al-Inany H. Acta Obstet Gynecol Scand 2001

Asherman syndrome—one century later

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The criteria for the diagnosis of Asherman syndrome;

I. At least one of the following clinical features;
   - ✓ Amenorrhea, hypomenorrhea
   - ✓ Subfertility, infertility
   - ✓ Recurrent pregnancy loss
   - ✓ History of abnormal placentation (previa, acreta…)

II. The presence of intrauterine adhesions by Hysteroscopy and/or histologically confirmed intrauterine fibrosis.

Dan Yu et al. Fertil Steril 2008

ETIOLOGY

I. Trauma to a gravid uterine cavity (%66.7)
   - ✓ Curettage (postpartum, postabortion, elective)
   - ✓ Cesarean section
   - ✓ Evacuation of hydatiform mole

II. Trauma to nongravid endometrium
   - ✓ (Diagnostic curettage, myomectomy, insertion of a IUD, operative hysteroscopy…)

III. Infection (chronic or subacute endometritis)

IV. Congenital anomaly of the uterus (esp. Septate uterus)

V. Genetic predisposition

Dan Yu et al. Fertil Steril 2008

CLASSIFICATION

European Society of Gynecological Endoscopy (ESGE) 1995

Grade	Extent of intrauterine adhesions[a]
I	**Thin or filmy adhesions** Easily ruptured by hysteroscope sheath alone Cornual areas normal
II	**Singular dense adhesion** Connecting separate areas of the uterine cavity Visualization of both tubal ostia possible Cannot be ruptured by hysteroscope sheath alone
IIa	**Occluding adhesions only in the region of the internal cervical os**[b] Upper uterine cavity normal
III	**Multiple dense adhesions** Connecting separate areas of the uterine cavity Unilateral obliteration of ostial areas of the tubes
IV	**Extensive dense adhesions with (partial) occlusion of the uterine cavity** Both tubal ostial areas (partially) occluded
Va	**Extensive endometrial scarring and fibrosis in combination with grade I or grade II adhesions** With amenorrhea or pronounced hypomenorrhea
Vb	**Extensive endometrial scarring and fibrosis** In combination with grade III or grade IV adhesions[b] With amenorrhea

Endoscopic surgery for Gynecologists, 1998

SYMPTOMATOLOGY

I. Menstrual abnormalities(%68)
II. Infertility (%43)
III. Recurrent pregnancy loss
IV. Other pregnancy complications
   - ✓ Spontaneous miscarriage
   - ✓ Preterm delivery
   - ✓ Abnormal placental implantation
   - ✓ Ektopic pregnancy
   - ✓ IUGR-?

Dan Yu et al. Fertil Steril 2008

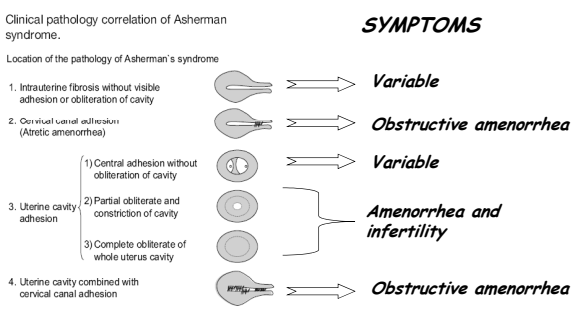
CLINICAL– PATHOLOGICAL CORRELATION

- ✓ The clinical features are closely associated with pathological findings in Asherman syndrome.
- ✓ These pathological findings are:
   - ✓ The depth of fibrosis
   - ✓ The location of the adhesions
   - ✓ The extent of the pathologic changes

Dan Yu et al. Fertil Steril 2008

CLINICAL– PATHOLOGICAL CORRELATION

Clinical pathology correlation of Asherman syndrome.



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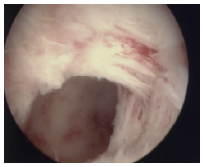
DIAGNOSIS

I. Radiological Diagnosis
- ✓ Hysterosalphingography
- ✓ Ultrasonography
- ✓ Sonohysterography
- ✓ MRI

USG

II. Hysteroscopy

H/S



IV Adhesions Management

AIM

- •Restoration of the uterine cavity
- •Prevention of recurrence
- •Endometrial restoration
- •Maintanence of the normal cavity

- •Adhesiolysis (H/S)
- •Lippes loop
- •High dose estrogen therapy
- •Follow up by H/S or HSG after treatment

PROCEDURE

TREATMENT

- ✓Expectant Management
- ✓Dilatation & Curettage
- ✓Hysterotomy
- ✓Hysteroscopy
  - ✓Because of its minimally invasive nature and also because it can be performed under direct vision ***"Hysteroscopy"*** is currently the gold standard for the treatment of intrauterine adhesions.

HYSTEROSCOPIC ADHESIOLYSIS

- ✓ *Adhesiolysis usually begins inferiorly and can be advanced until the uterine architecture has been restored. In most cases adhesiolysis can be performed by scissors or graspers but sometimes electrosurgery is needed.*

FERTILITY AND STERILITY®
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Hysteroscopic treatment of intrauterine adhesions is safe and effective in the restoration of normal menstruation and fertility

Recai Pabuçcu, M.D.
Vedat Atay, M.D.
Esat Orhon, M.D.
Bülent Urman, M.D.†
Ali Ergün, M.D.

- ✓ Hysteroscopic adhesiolysis is a safe and effective procedure for restoring the normal menstrual pattern and fertility.

Pabuçcu R., Fertil Steril, 1997

- ✓ Forty women with recurrent pregnacy loss or infertility resulting from intrauterine adhesions.
- ✓ After hysteroscopic adhesiolysis;
  - ✓ In 16 infertile cases;
    - ✓ %63 (n:10) conceived,
    - ✓ %37 (n:6) term or viable preterm delivery
  - ✓ In 24 cases with recurrent pregnancy loss;
    - ✓ %71 term or viable preterm delivery

Pabuçcu R., Fertil Steril, 1997

HYSTEROSCOPIC ADHESIOLYSIS

- ✓ ***Hysteroscopic adhesiolysis using scissors or biopsy forceps has the advantages of;***
  - ✓ Avoiding complications related to energy sources,
  - ✓ Minimizing the further destruction of the endometrium,
  - ✓ Decreasing the recurrent adhesion formation.

Fedele L, Acta Eur Fertil 1986
Feng ZC, Gynaecol Endosc 1999

HYSTEROSCOPIC ADHESIOLYSIS

- ✓ Hysteroscopic surgery using energy sources such as laser vaporization or electrodes provides effective and precise cutting as well as better hemostasis. But there is a possibility of further endometrial thermal damage

Duffy S, J Obstet Gynaecol 1992
Roge P, Gynaecol Endosc 1997

- ✓ However, other authors suggest that there is no difference between the use of scissors and resectoscope. Also electrosurgery achieves better hemostasis, thus providing an improved clarity of the operative field.

De Cherney A, Obstet Gynecol 1983
Cararach M, Human Reproduction 1994

Reproductive outcome following hysteroscopic adhesiolysis in patients with fertility due to Asherman's syndrome

- ✓ 89 patients with infertility due to Asherman syndrome
- ✓ Retrospective clinical analysis
- ✓ Hysteroscopic adhesiolysis by monopolar electrode knife
- ✓ A second look office hysteroscopy was performed in all cases after 2 months

Roy K et al. Arch Gynecol Obstet, 2010

Reproductive outcome following hysteroscopic adhesiolysis in patients with fertility due to Asherman's syndrome

- ✓ 12 patients showed reformation of adhesions and needed a repeat procedure
- ✓ Conception rate 40.4 %
- ✓ Live birth rate 86.1 %
- ✓ Miscarriage rate 11.1 %
- ✓ Hysteroscopic adhesiolysis is safe and effective for restoring menstrual function and fertility.

Roy K et al. Arch Gynecol Obstet, 2010

HYSTEROSCOPIC ADHESIOLYSIS

- ✓ Hysteroscopic management of the intrauterine adhesions, especially the severe and dense ones;
  - ✓ ***May be technically difficult,***
  - ✓ ***Also carries a significant risk of uterine perforation.***
- ✓ Perforation usually occurs during the dilatation of the cervical canal or / and the introduction of the hysteroscope.

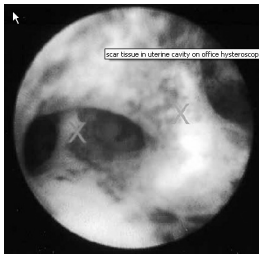
HYSTEROSCOPIC ADHESIOLYSIS

- ✓ In order to improve the safety and efficiency of the hysteroscopic adhesiolysis, and also to minimize the risk of uterine perforation the procedure can be guided by one of the following methods:
  - ✓Laparoscopy
  - ✓Transabdominal ultrasonography
  - ✓Fluoroscopic control
  - ✓Gynecoradiologic uterine resection

PREVENTION OF RECURRENT ADHESIONS

✓Because of the high rate of reformation of the adhesions (%3.1- 23.5), esp. the severe ones (%20-62.5) prevention after surgery is essential.

✓The risk is directly correlated with the type and the etiology of adhesions.



PREVENTION OF RECURRENT ADHESIONS

- ✓ ***Prevention of recurrent adhesions after surgery is essential for a successful treatment***

- ✓ ***Methods used for prevention:***
  I. Second / Third look hysteroscopic adhesiolysis
  II. Barrier Methods (Sepra film, hyaluronic acid gel, amnion graft)
  III. Mechanical Methods (IUD, Lippes loop, Foley baloon)
  IV. Hormone Treatment (estrogen, progestin, GnRH analogues, danazole)
  V. Pharmacologic Agents (antibiotics, NSAID, Ca antagonists, antihistaminics)

PREVENTION OF RECURRENT ADHESIONS

1) SERIAL HYSTEROSCOPY

✓Serial hysteroscopic adhesiolysis after primary treatment of intrauterine adhesions, is an effective method for the maintenance of the cavity as well as the prevention of recurrence.

Robinson JK et al. Fertil Steril 2008
Wheeler et al. Fertil Steril 1993

Postoperative adhesiolysis therapy for intrauterine adhesions (Asherman's syndrome)

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[a] Minimally Invasive Gynecologic Surgery Center, Newton-Wellesley Hospital, Newton; and [b] Brigham and Women's Hospital, Department of Obstetrics and Gynecology, Boston, Massachusetts

- ✓ ***AIM:*** To evaluate postoperative blunt adhesiolysis after sharp adhesiolysis for the treatment of intrauterine adhesions.
- ✓ ***DESIGN:*** Retrospective analysis of 24 patients treated with primary hysteroscopic adhesiolysis followed by hormone therapy and serial flexible office hysteroscopy.

Robinson JK et al. Fertil Steril 2008

✓Initial postoperative office hysteroscopies were performed within 2 weeks of the primary surgery. Subsequent hysteroscopies were performed every 1-3 weeks until minimal to no disease remained .

✓***RESULTS:***

- ✓Improvement in menstrual flow in 95%,
- ✓Relief of dysmenorrhea in 92% and,
- ✓%46 of fertility patients were actively pregnant or had delivered viable infants.

Conclusion(s): Blunt adhesiolysis with a flexible hysteroscope is effective for maintenance of cavity patency after primary treatment of intrauterine adhesions. (Fertil Steril® 2008;90:409–14. ©2008 by American Society for Reproductive Medicine.)

Robinson JK et al. Fertil Steril 2008

PREVENTION OF RECURRENT ADHESIONS

2) BARRIER METHODS

- ✓ ***Seprafilm,*** is a bioresorbable membrane of chemically modified hyaluronic acid and carboxymethylcellulose, was shown to be effective in reducing adhesion formation.
- ✓ Limited evidence that Seprafilm was effective in preventing adhesion formation following gynecological surgery for myomectomy (Cochrane Database Syst Rev 2008, CD000475)

The role of Seprafilm bioresorbable membrane in the prevention and therapy of endometrial synechiae

- ✓ 150 patients with incomplete or missed abortion undergoing D/C
- ✓ Seprafilm treatment n= 50, Control group n =100
- ✓ Synechiae was evaluated with HSG
- ✓ More than %90 of the patients where Seprafilm was used were adhesion free
- ✓ Intrauterine insertion of Seprafilm is safe and prevents the appearance of endocervical adhesions.
- ✓ Placement of Seprafilm; into the both cervical canal and endometrial cavity after suction evacuation or curettage for incomplete, missed and recurrent abortion, effectively prevents adhesion formation

Tsapanos et al. J Biomed Mater Res 2002

PREVENTION OF RECURRENT ADHESIONS

2) BARRIER METHODS

✓ *Auto-cross linked hyaluronic acid (ACP) gel*

✓ Hyaluronic acid is a natural component of the extracellular matrix and has been suggested as a possible adhesion barrier.

Effectiveness of auto-cross-linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis: a prospective, randomized, controlled study

- ✓ 92 patients with irregular menses and intrauterine adhesions
- ✓ Prospective randomized study
- ✓ Group A: H/S plus ACP gel n=43
- ✓ Group B : H/S n=41
- ✓ ACP gel reduces the development of IU adhesions.

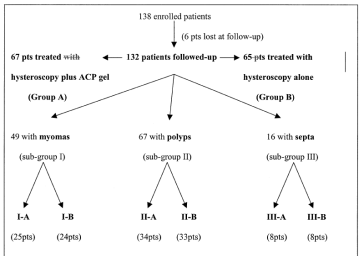
Table I. Patients' characteristics

Characteristic	Group A (ACP gel) (n = 43)	Group B (control) (n = 41)	Significance
Age (years) (± SD)	29.8 ± 4.1	30.7 ± 2.6	NS
Weight (kg) (means ± SD)	64.4 ± 4.6	62.8 ± 4.4	NS
Uterine size (hysterometry) (cm) (means ± SD)	6.9 ± 1.2	6.6 ± 1.5	NS
Parity	1.3 ± 0.2	1.5 ± 0.1	NS
Number of infertile patients	18	16	NS

NS = not significant.

Acunzo G et al. Hum Reprod 2003

Effectiveness of auto-crosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: a prospective, randomized, controlled study



De Guida M et al. Hum Reprod 2004

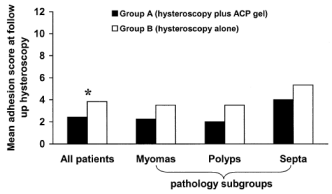
ACP gel= auto-crosslinked hyaluronic acid gel

Group A: patients were treated with hysteroscopy plus ACP gel (10 ml)

Group B: patients underwent hysteroscopy alone (control group)

Auto-cross linked hyaluronic acid (ACP) gel

✓ After hysteroscopic adhesiolysis intracavitary ACP gel application, effectively prevents postoperative adhesion formation.



De Guida M et al. Hum Reprod 2004

Interest of auto-cross-linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: a case control study

✓ 54 cases with IU lesions
✓ Group A n=30 H/S plus hyaluronic acid gel
✓ Group B n=24 H/S
✓ No difference in IU adhesion formation.

Ducarme G, et al. J Obstet Biol Reprod 2006

PREVENTION OF RECURRENT ADHESIONS

2) BARRIER METHODS

- ✓ *Amnion Graft*
- ✓ Fresh amnion graft draped over an inflated Foley catheter balloon

Amnion graft following hysteroscopic lysis of intrauterine adhesions

- ✓ Hysteroscopic adhesiolysis was followed by introduction of fresh amnion graft draped over an inflated Foley catheter balloon in 25 patients.
- ✓ Repeat hysteroscopy showed further adhesion formation in 48% but all these were minimal.
- ✓ Long-term data are not available

Amer MI et al, J Obset Gynecol Res, 2006

Human amnion as a temporary biologic barrier after hysteroscopic lysis of severe intrauterine adhesions, pilot study

- ✓ 45 patients with severe intrauterine adhesions
- ✓ Group 1 n=15 intrauterine balloon
- ✓ Group 2 n= 15 fresh amniotic graft
- ✓ Group 3 n=15 dried amnion graft for 2 weeks
- ✓ H/S 2-4 months postop.
- ✓ Significant improvement in adhesion graft vs IU balloon. Greater improvement with fresh amnion

Amer et al., 2010, J Min Inv Gynecol

PREVENTION OF RECURRENT ADHESIONS

2) BARRIER METHODS

Amnion graft is a promising adjunctive procedure for decreasing recurrence of adhesions and encouraging endometrial regeneration.

PREVENTION OF RECURRENT ADHESIONS

3) MECHANICAL METHODS

- ✓ Some studies reported that the application of a 8 – 10 F Foley catheter into the uterine cavity with an inflated balloon for several days after adhesiolysis may prevent recurrence.

Orhue AA et al. Int J Gynaecol Obstet 2003
Amer MI et al. MEFS J 2005

PREVENTION OF RECURRENT ADHESIONS

3) MECHANICAL METHODS

- ✓ In a comparative study, after lysis of adhesions either a 10 F Foley catheter balloon, inflated with 3,5 ml of saline was left in the uterine cavity for 10 days or Lippes loop was placed for 3 months.
- ✓ Foley catheter resulted in a greater proportion of women achieving normal menses(81% vs 63%), higher conception rates (34% vs 23%)and a reduced need for reoperation.

Orhue AA et al. Int J Gynaecol Obstet 2003

PREVENTION OF RECURRENT ADHESIONS

3) MECHANICAL METHODS

- ✓ For many years, the placement of an IUD into the uterine cavity for 3 months has been considered the standard method of maintaining the uterine cavity after surgery.
- ✓ However, the copper-bearing IUDs might induce an excessive inflammatory reaction and T-shaped coils may have a too small surface area to maintain the uterine cavity.
- ✓ Some authors suggested that larger inert devices such as Lippes-loop is effective in the prevention of recurrent adhesions.

March CM. Obstet Gynecol Clin North Am 1995
Orhue AA et al. Int J Gynaecol Obstet 2003
Pabuccu et al., Fertil Steril 2008

Efficiency and pregnancy outcome of serial intrauterine device–guided hysteroscopic adhesiolysis of intrauterine synechiae

- ✓ Prospective, randomized trial to highlight the efficiency of Lippes loop guidance during hysteroscopic adhesiolysis for severe adhesions.
- ✓ 71 subfertile patients with severe intrauterine adhesions.
- ✓ Patients were randomized into 2 groups;
  - ✓ Group 1: Just after hysteroscopic adhesiolysis, IUD was inserted and 1 week later a second look H/S was performed for further lysis by the guidance of IUD. (n=36)
  - ✓ Group 2: Just after hysteroscopic adhesiolysis, IUD was inserted and the patients were given estrogen+progesterone for 2 months.(n=35)

Pabuccu et al., Fertil Steril 2008

✓ An IUD-guided therapeutic approach simplifies hysteroscopic adhesiolysis for severe intrauterine adhesions. The Lippes loop IUD probably enlarges the cavity and creates bits of endometrium, which simplifies the procedure for adhesiolysis.

Adhesion formation results.

	Group 1 (n = 36)		Group 2 (n = 35)
Result	One wk after hysteroscopy	Two mo after hysteroscopy	Two mo after hysteroscopy
None	5 (13.5)	33 (89.1)[b]	6 (17.1)
Filmy	12 (32.4)	1 (2.7)[b]	11 (31.3)
Mild	15 (40.5)	1 (2.7)[b]	13 (37.0)
Severe	4 (10.8)	1 (2.7)[b]	5 (14.2)

Note: Data are n (%).
[a] $P < .05$, statistically significant.
[b] $P < .01$, statistically significant.

Pabuccu. IUD-guided adhesiolysis. Fertil Steril 2008.

Pabuccu et al., Fertil Steril 2008

✓ *However, spontaneous pregnancy and live birth rates between the two groups were not statistically significant.*

Comparison of patient reproductive outcomes.

Parameter	Group 1 (n = 36)	Group 2 (n = 35)
Spontaneous pregnancies		
Pregnancy rate	17/36 (47.2)	11/35 (30)
Live birth rate	10/36 (28)	7/35 (20)
ART cycle pregnancies		
Pregnancy rate	5/11 (45)	4/13 (30)
Live birth rate	3/11 (27)	2/13 (15)

Note: Data are n (%). ART = assisted reproductive technology.

Pabuccu. IUD-guided adhesiolysis. Fertil Steril 2008.

Pabuccu et al., Fertil Steril 2008

PREVENTION OF RECURRENT ADHESIONS

4) HORMONE TREATMENT

✓ Estrogen-progestin therapy significantly increases endometrial thickness and volume, but there is no objective evidence based on randomized, controlled trials to confirm the efficacy of hormone treatment on the reduction of reformation of intrauterine adhesions.

Dan Yu et al. Fertil Steril 2008

CONCLUSION

✓ ***"HYSTEROSCOPY"*** is the gold standard for diagnosis and treatment of intrauterine adhesions.

✓ Prevention of recurrent adhesions after surgery is essential for a successful treatment.

✓ There is still no single modality proven to be unequivocally effective in preventing postoperative adhesion formation after hysteroscopic surgery.