Overview and Treatment: Hysteroscopic Techniques

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9.1 Overview

Intrauterine adhesions have been recognized as a cause of secondary amenorrhea since the end of the nineteenth century [1].

More than a century ago, H. Fritsch [1] first reported a case of post-traumatic intrauterine adhesion and in the mid-twentieth century, Stamer [2] reviewed the literature and added 24 cases of his own with intrauterine adhesions associated with gravid uterus.

In 1948, Joseph G. Asherman further described the eponymous condition with a series of papers [3–6] about frequency, etiology, symptoms, and roentgenologic picture of this condition.

The terms "Asherman's syndrome" (AS) and intrauterine adhesions (IUAs) are often used interchangeably, although the syndrome requires the constellation of signs and symptoms (pain, menstrual disturbance, and subfertility in any combination) related to the presence of IUAs; the presence of IUAs in the absence of symptoms is of questionable clinical significance.

Asherman's syndrome has an impact on both reproductive outcomes and gynecologic symptoms and invariably may affect patients' physical and psychosocial health; while understanding and preventing the causes of intrauterine adhesions are

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sometimes challenging, the correct surgical management is often successful in restoring physiology and offers favorable fertility outcomes; in retrospective cohort studies including patients with AS treated with adhesiolysis, rates of successful restoration of menses and cavity anatomy are greater than 95%.

Substantial progress has been made since the Asherman's report: large-scale series, although retrospective, have reported clinical outcomes while randomized controlled trials (RCTs) have investigated both primary and secondary adhesion prevention including solid and semisolid barriers.

Prevention of re-formation of adhesions is still debated as no single method for preventing recurrence has shown superiority while recent human studies documenting successful pregnancy outcomes after stem cell treatments following intermittent hysteroscopy are reported.

Although some new therapeutic approaches hold promise for future, hysteroscopic management with lysis of adhesions remains the gold standard for diagnosis and treatment and surely adopting an office-based approach offers several advantages.

9.2 Epidemiology

Accurate incidence of IUAs is difficult to ascertain, as few studies assess the occurrence of adhesion formation in a prospective fashion.

Another conundrum is that Asherman's syndrome may go unrecognized in women who are not trying to conceive since they may not recognize or be concerned with the symptoms such as hypomenorrhea. On the other hand, this clinical condition may be underdiagnosed because it is usually undetectable by routine examinations or diagnostic procedures such as an ultrasound scan.

Prevalence ranges from 0.3% as an incidental finding in women undergoing IUD placement to ≥20% in women with a history of postpartum curettage and the number of cases reported has been increasing with the widespread use of hysteroscopy and improvement of imaging tools concentrating on intrauterine pathology.

It is found in 1.5% of women evaluated with a hysterosalpingogram (HSG) for infertility, between 5% and 39% of women with recurrent miscarriage [7].

It may occur in up to 13% of women undergoing a termination of pregnancy during the first trimester, and 30% in women undergoing a dilation and curettage (D and C) after a late spontaneous abortion.

9.3 Etiology and Pathophysiology

The formation of adhesions in an organ that routinely undergoes cyclical change with growth and sloughing is not well understood: intrauterine adhesions (IUAs) are believed to form following a process that damages the basalis layer of the endometrium [8] and the gravid uterus seems particularly susceptible (Table 9.1).

Table 9.1 D&C, dilation and curettage; POC, products of conception; SAB, spontaneous abortion; TOP, termination of pregnancy

Condition	Procedure	Incidence (%)	References
Gravid			
SAB	Suction D&C	15	Gilman et al.
		19	Hooker et al.
First-trimester TOP	Suction D&C	21	Hooker et al.
Retained POC	Hysteroscopic resection	6	Smorgick et al.
		13	Hooker et al.
		19	Barel et al.
	Suction D&C	30	Hooker et al.
Gynecologic			
Septum	Hysteroscopic resection	24	Yu et al.
Fibroids	Hysteroscopic myomectomy	8	Touboul et al.
	Abdominal myomectomy	22	Bhandari et al.

From Salazar CA et al. (2017)

Studying a population of women with confirmation of a normal uterine cavity at baseline, Gilman et al. [9] reported a 15% incidence of IUA formation after suction dilation and curettage by a hysteroscopic follow-up in the ensuing 2–4 months for management of spontaneous abortion (SAB) vs. 1.2% with expectant medical management.

These data are similar to those reported in other papers; a recent systematic meta-analysis reported a similar pooled prevalence of 19% amongst women who suffered a miscarriage and were prospectively assessed by hysteroscopy within 12 months, with over half of the reported cases described as mild adhesive disease [10].

Moreover, the risk and extent of adhesion formation may differ depending on the timing of instrumentation, during early pregnancy versus the postpartum period. Thus up to 21% of women evaluated by hysteroscopy following first-trimester termination of pregnancy shows the formation of a certain degree of IUAs [11].

In one study of women with IUAs, 70% of patients with severe Asherman's had prior instrumentation in the postpartum period, whereas 80–90% of patients with mild Asherman's had procedures performed in the first trimester of pregnancy [12].

Formation of IUA has also been associated with retained products of conception (RPOC) [13]. Amongst women surgically treated for RPOC and evaluated hysteroscopically afterwards, the overall incidence of IUAs varies widely in literature ranging from 6% to 22% [14, 15]. Those treated surgically with dilatation and curettage seem more likely to suffer from IUAs compared to women treated with hysteroscopic resection for RPOC [14]; besides hysteroscopic treatment of RPOC looks to be an opportunity to maximize successful fertility outcomes [16].

IUAs can obviously also develop after gynecologic procedures, such as after resection of uterine septa and leiomyomas.

A large prospective study by Yu et al. [17] evaluating with a second-look hysteroscopy 238 patients previously undergoing hysteroscopic treatment of

uterine septa using bipolar energy reported an incidence of IUAs of ≈20%, while newer data regarding incidence of IUA after hysteroscopic myomectomy reveal that the incidence of de novo adhesion formation is less than 10% [14]. This is in contrast to older data reporting rates of adhesion occurring as high as 30–45% [18].

A recent prospective study reported rates of IUA re-formation nearing 22% for abdominal myomectomy procedures as diagnosed by hysteroscopy 3 months after their surgical procedure [19].

Understanding the related molecular mechanisms regulating the pathogenesis of intrauterine adhesions could be the keystone for the prevention of de novo formation and recrudescence and treatment.

It has been reported that postinfectious inflammation and inflammatory factors play important roles in the pathogenesis of AS [2–4, 20–23].

IUAs are in addition caused by infection or injury-related inflammation. It coordinates gene expression and controls the tissue microenvironment especially with cytokines such as TGF-β, TNF-α, IL-1, and IL-18, frequently elevated in intrauterine adhesions, and promoting the pathogenesis of Asherman's syndrome [24].

The nuclear factor-kappaB (NF-κB) transcription factor promotes the expression of intrauterine adhesion inflammatory factors and plays a central role in inflammatory diseases [5, 6, 25–27], and is significantly elevated in endometrial samples from intrauterine adhesion patients compared to normal endometrium controls in human and murine models [24].

However, whether NF-κB promotes the pathogenesis of Asherman's syndrome remains unknown.

9.4 Clinical Presentation

The classic presentation of Asherman's syndrome is an ovulatory patient with onset of secondary amenorrhea after uterine surgery on a gravid uterus and a history of failed provocation of withdrawal bleeding after progesterone administration.

The largest published series to date on the outcomes of hysteroscopic adhesiolysis for Asherman's syndrome reported two-thirds of patients presenting with amenorrhea, while nearly one-third complaining hypomenorrhea (i.e., diminished menstrual flow) [12]. Approximately 3.5% of patients have a primary complaint of cyclic dysmenorrhea. However, menstrual pattern and extent of IUA do not always correlate linearly as a small number of patients (2–5%) may present with regular, painless menses of normal flow and duration despite a severe disease [18].

An ultrasound will demonstrate a hematometra if there are dense lower uterine segment adhesions or cervical adhesions that cause menstrual outflow obstruction; notably, in patients with severe Asherman's syndrome, the increased connective tissue fibrotic and atrophic changes can result in an absence of hematometra despite outflow obstruction [28].

In addition to symptoms of amenorrhea, hypomenorrhea, and cyclical pain, IUA can be associated with infertility and recurrent pregnancy loss.

Synechiae can obstruct the tubal ostia and adhesions may diminish the viable endometrial surface so approximately 7% of patients can present with a primary fertility complaint [12].

IUA can also be asymptomatic, but still may have a negative impact on fertility.

9.5 Workup

In women with suspected Asherman's syndrome, physical examination frequently fails to reveal abnormalities and office ultrasound often fails to detect any aberration.

According to AAGL/ESGE latest practice guidelines (2017) **hysteroscopy** is the most accurate method for diagnosis of IUAs and should be the investigation of choice when available (level of evidence B), as it provides several **advantages**:

1. A real-time view of the cavity
2. Enables accurate description of location and degree of adhesions
3. Precise classification
4. Concurrent treatment of IUAs (*see and treat*)

When hysteroscopy is not available, hysterosalpingography (HSG) and sonohysterography (SHG) with saline infusion sonography (SIS) or gel infusion sonography (GIS) are reasonable alternatives.

Sonohysterography (SHG; also called saline infusion sonography [SIS] or gel infusion sonography [GIS]) was found to be as effective as HSG, with both reported to have a sensitivity of 75% and positive predictive value of 43% for SHG or SIS/GIS and 50% for HSG, compared with hysteroscopy [10, 14]. Three-dimensional SHG has a high specificity of 87% although a lower sensitivity of 70% when compared with the standard hysteroscopy [16].

Magnetic resonance imaging (MRI) for the diagnosis of IUAs is a money- and time-consuming alternative [1, 3, 29–32] and as a matter of fact it is not recommended for clinical practice outside of clinical research studies (Level C) until further research is undertaken.

9.6 Classification System

To date the presence of various classification systems is quite puzzling given the fact that there have been no comparative analyses of the different classifications as the extreme heterogeneity makes appraisal between different series difficult to interpret.

Societies do not endorse any specific system given the deficiencies in each of the following but surely almost all are based on hysteroscopic assessment making this procedure essential since the diagnostic workup.

In the late 1970s, March proposed the first idea for classification based on hysteroscopic findings reporting a series of 66 patients undergoing hysteroscopic evaluation and treatment for Asherman's syndrome.

The idea was to divide those patients using the proportion of cavity interested by adhesions and the characteristics of the findings as follows:

- Severe: >3/4 of uterine cavity is involved; agglutination of walls or thick bands; ostial areas and upper cavity occluded
- Moderate: 1/4 to 3/4 of uterine cavity involved; no agglutination of walls and adhesions only; ostial areas and upper fundus only partially occluded
- Minimal: <1/4 of uterine cavity involved; thin or filmy adhesions; ostial areas and upper fundus minimally involved or clear

Also Professor J. Hamou, the father of modern hysteroscopy, proposed his own way in order to make a reproducible description classifying adhesions as isthmic, marginal, central, or severe according to hysteroscopic assessment.

With the advances in technology and the introduction of new diagnostic tools some authors also included HSG assessment as a combination of hysteroscopic findings or alone when hysteroscopy is not available: hysteroscopy remains a mainstay.

For example European Society of Hysteroscopy [29], American Fertility Society [30], and AAGL grade the clinical findings also accepting a combination of hysteroscopic and HSG findings as a reasonable alternative.

As a matter of fact, the great part of these classifications use hysteroscopic criteria (Table 9.2) and define a scoring system according to the extent of the cavity involvement and/or the severity of the synechiae and/or the extent of occlusion (partial or total).

Table 9.2 Classification of intrauterine adhesions

Source	Summary of classification
March et al.	Adhesions classified as minimal, moderate, or severe based on hysteroscopic assessment of the degree of uterine cavity involvement
Hamou et al.	Adhesions classified as isthmic, marginal, central, or severe according to hysteroscopic assessment
Valle and Sciarra	Adhesions classified as mild, moderate, or severe according to hysteroscopic assessment and extent of occlusion (partial or total) at HSG
European Society of Hysteroscopy	Complex system classifies IUAs as grades I through IV with several subtypes and incorporates a combination of hysteroscopic and HSG findings and clinical symptoms
American Fertility Society	Complex scored system of mild, moderate, or severe IUAs based on the extent of endometrial cavity obliteration, appearance of adhesions, and patient menstrual characteristics based on hysteroscopic or HSG assessment
Donnez and Nisolle	Adhesions classified into six grades on the basis of location, with postoperative pregnancy rate the primary driver. Hysteroscopy or HSG is used for assessment
Nasr et al.	Complex system creates a prognostic score by incorporating menstrual and obstetric history with IUA findings at hysteroscopic assessment

From AAGL practice guidelines on intrauterine adhesions

A commonly used system in the United States is the three-pronged approach provided by the American Society for Reproductive Medicine (ASRM), which defines the severity of intrauterine adhesive disease based on the extent of cavity involvement (<1/3, 1/3 to 2/3, >2/3), the type of adhesion seen (filmy, filmy and dense, dense), as well as the menstrual pattern (normal, hypomenorrhea, amenorrhea). Points are assigned to each finding and the patient is staged from 1 to 3 corresponding to mild, moderate, or severe, based on the total score [33]. The classification system is useful; however, it lacks power in that the staging does not necessarily correlate directly with clinical prognosis [34].

Some other classifications may include other variables such as menstrual and obstetric anamnesis with the findings at the hysteroscopy.

9.7 Treatment

Although a broadly accepted surgical and postoperative flowchart for the management of Asherman's syndrome is difficult to assess, recent American Association of Gynecologic Laparoscopists (AAGL) practice guidelines suggest that high-quality studies and larger case series should be undertaken to provide a more accurate assessment of outcome measures and finally improve the management of this condition.

9.7.1 Hysteroscopic Adhesiolysis

Lysis of intrauterine adhesions under direct hysteroscopic visualization is generally regarded as the mainstay of treatment for Asherman's syndrome; however successful treatment is often difficult to achieve mostly because of the high recurrence rate after hysteroscopic adhesiolysis that is essentially related to the extent and severity of any preexisting lesion and is reported to reach two-thirds in severe cases, more than 20% in moderate cases, and negligible percentages for mild synechiae [35–38].

Hysteroscopic guidance has several advantages:

- Hysteroscopy enables lysis of adhesions under direct visualization and magnification.
- Cavity distension and separation of the uterine walls place bands of fibrosis under tension and this facilitates lysis of adhesions.
- The surgeon can bluntly lyse filmy adhesions (especially central cavity lesions) simply exploiting cavity distension and using the tip of the hysteroscope without any other instrument.
- Operating channels of hysteroscopes can allow various instruments to be used for lysis of firm adhesions: scissors, monopolar energy systems, bipolar energy systems, or neodymium-doped yttrium aluminum garnet [Nd-YAG] laser allows the surgeon bloodless excision also in severe situations.

The basic principle involves beginning adhesiolysis in a caudad to cephalad fashion towards the uterine fundus to enable cavity expansion by the distension media.

The lysis of filmy and central synechiae should be performed first as they are more easily distinguishable; dense synechiae and those of marginal location should be taken down last as they are technically harder to resect and can result in a higher chance of bleeding, complications, and uterine perforation.

The surgeon must remember to lyse the median and avascular portion of the synechiae and both ends will immediately retract into the thickness of the wall leaving behind only two small residual areas on opposing walls of the uterine cavity. The operator usually only needs to move the tip of the hysteroscope to tear down the thinner synechiae while it is not enough to solve the thickest.

In fact, lysis of moderate synechiae often requires the use of hysteroscopic scissors to gradually transect fibrous bridges. The absence of nerve endings or blood vessels in fibrous tissue allows to perform lysis without causing pain or bleeding, which otherwise would impair vision. The major advantage of scissors is their extreme delicacy leaving healthy endometrium untouched. This can decrease the risk for further damage and reduce the risk of recurrence. Additionally, the lack of coagulation while dissecting with scissors can be used to the surgeon's advantage while determining when to stop resection at the uterine fundus. Slight bleeding at the fundus indicates entry into myometrium, a phenomenon that is masked if instruments with coagulation capacity are used.

Severe synechiae may be treated using bipolar electrodes always cutting at the level of the avascular median plane. The use of modern bipolar electrodes, which have a limited surface of exposure to the current, inherently reduces the risk of iatrogenic thermal damage to adjacent healthy endometrium. Another advantage of electrosurgical systems over hysteroscopic scissors is that they cut and also coagulate, thus yielding a better outcome in terms of hemostatic control.

Monopolar instruments require nonelectrolyte distending media like glycine and sorbitol. Excessive absorption of these hypotonic media can lead to hypo-osmolality and hyponatremia, and in extreme cases cerebral edema. The main advantage of this modality is precise and hemostatic resection of disease. The procedure is hence best performed under experienced hands where time management and efficiency of movement in the surgical field are of paramount importance.

Bipolar vaporization of adhesive disease in the uterine cavity using the Versapoint (GYNECARE VERSAPOINT™ Bipolar Electrosurgery System, Johnson & Johnson) instrument has been described. The advantage over monopolar instruments is the fact that these instruments use normal saline isotonic distention media. Even though excessive fluid deficit with normal saline can result in hypervolemia, pulmonary edema, and congestive heart failure, these complications are typically seen at a fluid deficit of >2500 mL and most can be reversed by induced diuresis [39].

Hanstede et al. [40] reported a series of hysteroscopic adhesiolysis performed in 638 patients as a result of a 10-year centralized Asherman's surgery. At the follow-up despite the high proportion of severe cases (60%) a healthy menstrual pattern

was restored in 624 (97.8%) within 2 months after initial surgery with an overall success rate (restoration of menses and cavity anatomy) of 95.0% in 1–3 attempts.

From early 1990s onwards most studies reported discordant data with a complete normalization of uterine cavity ranging from 43.7% to 93.3% and restoration of menses ranging from 67.7% to 96% sample sizes. These series are sometimes poorly comparable as they come from a collection of retrospective data and with nonhomogeneous severity of IUAs and consistent biases in population selection [41–50].

Some ancillary techniques have been described to improve the safety in difficult cases of hysteroscopic adhesiolysis (typically with severe occlusive disease) such as the following:

Instillation of methylene blue dye to stain the endometrium and guide the surgeon in between areas of fibrosis as the dye stains endometrium well but uptake into myometrium is not seen.

Transabdominal ultrasound guidance can help to reduce the risk of uterine perforation [23, 28]. The availability and familiarity of sonography to gynecologists make this option easy to implement. Still, uterine perforations in as many as 5% of cases have been reported.

Fluoroscopic guided resection: Fluoroscopic guidance allows the surgeon to view islands of endometrium behind scar tissue in an obliterated uterine cavity. This technique has also been described as an outpatient procedure, though further study is needed [42, 51].

Laparoscopic guided resection: Laparoscopic guidance for severe cases of intrauterine adhesiolysis has been advocated for immediate recognition and treatment of uterine perforation and minimizing extrauterine trauma.

9.7.2 Office Hysteroscopy

Although outpatient hysteroscopy has been gaining popularity rapidly, little data have been reported on the treatment of Asherman's syndrome in this setting.

Outpatient hysteroscopy presents an alternative to traditional hysteroscopy performed in the operating room and offers advantages in terms of reduced anesthetic risks, improved postoperative pain control, faster return to work, and decreased cost [52–60].

Large case series have reported excellent success rates with minimal complications [56–60]. Patients generally report high satisfaction with their procedures performed in an outpatient setting [40] and some have suggested that intrauterine lysis of adhesions can also be performed in this setting [56, 59, 60].

Literature evaluating the feasibility and success rates of treating Asherman's syndrome in outpatient hysteroscopy units shows that surgical treatment may be performed in an office setting with outcomes similar to those in inpatient settings.

Bougie et al. [32] reviewed their data on patients treated in the outpatient hysteroscopy suite at Ottawa Hospital from 2008 to 2013. Patients had regular follow-up clinic appointments after their procedure in order to assess a series of clinical

endpoints (regular menses, pregnancy rates). Only 2 out of 19 patients (10%) required hysteroscopic adhesiolysis performed in the main operating room as they required hysteroscopic myomectomy as an adjunct procedure, which could not be performed in the office setting.

The first obvious advantage of the office setting is in regard to the analgesia methods used during each procedure: it is possible to perform even complex procedures with the administration of NSAIDs preoperatively sparing the side effects of intravenous sedation with the use of fentanyl and/or midazolam or more invasive techniques as the paracervical blocks.

Another clear advantage is that we can bring back patients to repeat hysteroscopies until either no adhesions or only mild adhesions are noted. The rationale for this management approach is [32, 61] that repeated adhesiolysis with office hysteroscope allows for the release of thin, filmy adhesions before they have the chance to become dense and/or vascularize and so to prevent recurrence of intrauterine adhesions.

9.8 Postoperative Management

The lack of consensus with regard to the use of postoperative adjuvant treatment to prevent adhesion re-formation and the paucity of well-planned RCT in this area is obvious.

Attention should be focused on reducing the risk of re-formation of IUAs.

Various methods have been described in literature:

- Solid barriers
- Semisolid barriers
- Hormone therapy
- Antibiotics
- Stem cells

Tertiary referral centers which manage a high volume of cases should be encouraged to set up a registry to facilitate the collection of valuable audit data and to conduct RCT to examine the effectiveness, if any, of the various adjuvant treatments in the prevention of recurrence.

9.8.1 Solid Barriers

IUD insertion after hysteroscopic treatment has been described for many years. However, data to support its effectiveness is lacking.

The type of IUD inserted may be important. Copper-containing and T-shaped IUDs cannot be recommended because of their inflammatory provoking properties and small surface area, respectively. Moreover, copper IUD can provoke inflammation and may be counterproductive [62, 63].

The risk of infection after IUD insertion postsurgical resection of IUAs is estimated to be 8% and perforation of the uterus during IUD insertion has been anecdotally reported. The risk of infection when an IUD is introduced into the uterus immediately after adhesiolysis is estimated to be 8%, and perforation of the uterus during IUD insertion has been reported [62–64].

There are few studies comparing IUD use to intrauterine balloon, Foley catheter, and other treatment options such as hormone treatment and barriers like amniotic membranes with low/very-low-quality and underpowered sample sizes, significant heterogeneity, and high risk of biases.

Despite adhesion re-formation being recognized as a biological process that develops over a relatively prolonged period of time, recently the intermittent use of intrauterine balloon dilatation under ultrasound guidance in the postoperative period has been proposed.

9.8.2 Semisolid Barriers

A number of gel adhesion barriers may be suitable for preventing IUAs: auto-cross-linked hyaluronic acid gel, modified hyaluronic acid, fresh amnion, and dry amniotic membranes have been used as an adhesion barrier [76–80, 82].

Data from animal (rabbits) studies are encouraging and report increasing pregnancy rates when hyaluronic acid barriers are used following induced IUAs, but the same fertility data following treatment with a gel barrier in human is still lacking even if auto-cross-linked hyaluronic acid gel shows an advantage when compared to observation alone in preventing re-formation of IUAs at a second-look hysteroscopy.

However a retrospective series found the reduction to be significantly greater in those women using balloon compared with IUD, hyaluronic gel, and observation alone ($p = 0.001$).

Fresh and dry amniotic grafts have been used as an adhesion barrier with fresh amnion showing better results in pilot studies. The complementary use of fresh amnion graft with a Foley catheter has been described.

A recent meta-analysis on the complementary use of amnion graft with an intrauterine catheter showed that amniotic membrane treatment increased the menstrual blood volume after hysteroscopic adhesiolysis with no statistically significant difference in terms of obstetrical outcomes (pregnancy and spontaneous abortion rates) [71–75].

9.8.3 Hormone Therapy

Postoperative treatment with estrogen therapy (e.g., daily conjugated equine estrogen with or without opposing progestin) has not been standardized in terms of dosage, duration, administration route, or combination with progesterone, as data on its cost-effectiveness are scarce (Table 9.3).

Table 9.3 Summary of the various doses of postoperative estrogen therapy used by different investigators after intrauterine adhesiolysis

Type	Daily dose	Duration	Pattern	References
E2	2 mg	2 months	Continuous	Roy et al. (2010) [86]
	4 mg	2 months	Cyclical	Zikopoulos et al. (2004) [77]
		2 months	Continuous	Capella-Allouc, et al. (1999) [35]
		2 months	Continuous	Fernandez et al. (2006) [76]
	4–6 mg	4–10 weeks	Continuous	Myers et al. (2012) [87]
	6 mg	6 weeks	Continuous	Malhotra et al. (2012) [88]
	7.5 mg	2 months	Continuous	March et al. (1976) [27]
	10 mg	3 months	Cyclical	Liu et al. (2016) [89]
	12 mg	3 months	Cyclical	Orhue et al. (2003) [57]
CEE	0.625 mg	14 days	Cyclical	Yasmin et al. (2007) [40]
		1 month	Cyclical	Takai et al. (2015) [90]
		3–4 months	Continuous	Protopapas et al. (1998) [91]
	1.875 mg	60 days	Continuous	Chen et al. (1997) [92]
	2.5 mg	1 month	Cyclical	Amer et al. (2006) [63]
		1 month	Cyclical	Robinson et al. (2008) [38]
		3 weeks	Continuous	Thomson et al. (2007) [41]
	4 mg	2 weeks	Cyclical	Knopman et al. (2005) [93]
		3 months	Cyclical	Salma et al. (2011) [94]
	5 mg	2 months	Cyclical	Pabuccu et al. (2008) [79]
Vaginal micronized E2	6 mg	4 weeks	Cyclical	Dawood et al. (2010) [95]

Adapted from Liu L. et al. 2018

9.8.4 Antibiotics

The concept that infection may be a leading cause of IUA formation has led many surgeons to treat women undergoing surgical lysis of IUAs with preoperative or intraoperative antibiotic therapy, and some continue with postoperative antibiotic therapy in order to reduce the theoretic risk of secondary infection. There are no data regarding the routine use of antibiotics before, during, or after surgical lysis of intrauterine adhesions. Even the American College of Obstetricians and Gynecologists (ACOG) guidelines for antibiotic use in gynecologic procedures do not support antibiotic use for diagnostic or operative hysteroscopy [76].

9.8.5 Stem Cells

Because mesenchymal progenitor cells have various functions that depend on the tissue origin and donor, it is now accepted that human stem cells will be available as cell sources in regenerative medicine. These cells showed their therapeutic contributors in murine models of Asherman's syndrome as they can significantly improve reproductive outcomes.

More recently, the use of stem cell therapy to help regenerate the endometrium holds promise also in humans. Autologous adult BMSC transplantation has been reported to result in regenerating injured endometrium not responding to conventional treatment for AS.

In one report all 16 women treated with uterine intravascular infusions of bone marrow-derived stem cells had return of menses after adhesiolysis, with three spontaneous pregnancies and another seven pregnancies with in vitro fertilization.

As stated by AAGL guidelines it is imperative that well-conducted RCTs are performed to establish the role of stem cells in addition to or independent of surgical treatments before it is made available in our clinical practice.

Our lack of understating of the molecular pathophysiology of intrauterine adhesions has caused a major hurdle in reaching a goal of complete cure mostly in the field of secondary prevention. While surgical management is gaining finesse, on the other hand prevention of recurrences is the perennial object of dispute while the application of contemporary technologies opens unexploited avenues to innovative therapy [77–80].

The joint AAGL and ESGE guidelines also included recommendation for the prevention of adhesion re-formation. The only methods to receive a Level A grade were the solid barriers and semisolid barriers listed above (Table 9.4).

Table 9.4 Guidelines for secondary prevention of intrauterine adhesions

	Statement
1.	The use of an IUD, stent, or catheter appears to reduce the rate of postoperative adhesion re-formation. There are limited data regarding subsequent fertility outcomes when these barriers are used.
2.	The risk of infection appears to be minimal when a solid barrier is used compared with no treatment.
3.	There is no evidence to support or refute the use of preoperative, intraoperative, or postoperative antibiotic therapy in surgical treatment of IUAs.
4.	If an IUD is used postoperatively, it should be inert and have a large surface area such as a Lippes loop. Intrauterine devices that contain progestin or copper should not be used after surgical division of IUAs.
5.	Semisolid barriers such as hyaluronic acid and auto-cross-linked hyaluronic acid gel reduce adhesion re-formation. At this time, their effect on post-treatment pregnancy rates is unknown.
6.	Following hysteroscopic directed adhesiolysis, postoperative hormone treatment using estrogen, with or without progestin, may reduce recurrence of IUAs.
7.	The role of medications designed as adjuvants to improve vascular flow to the endometrium has not been established. Consequently, they should not be used outside of rigorous research protocols.
8.	Stem cell treatment may ultimately provide an effective adjuvant approach to the treatment of Asherman's syndrome; however, evidence is very limited and this treatment should not be offered outside of rigorous research protocols.

9.9 Prognosis

Even if it is not a life-threatening condition, AS surely affects quality of life as the reproductive outcome after hysteroscopic adhesiolysis in women with AS has been reported in a number of studies and the reported pregnancy rate after hysteroscopic management ranges from 10.5% to 100%.

The results are variable due to a number of biases: firstly, the confounding variables including the age of the subjects, the severity of the IUA, the duration of follow-up, and the coexistence of any other infertility factors and then many of the reported studies that consisted of small numbers with a relatively wide confidence interval.

Recently a systematic review of literature based on 54 studies including nearly 4600 women found a certain relationship between the severity of adhesion and pregnancy rate: amongst women with mild, moderate, and severe IUA, the median pregnancy rates were 69.1%, 61.3%, and 44.3%, respectively, and the pregnant rate was significantly decreased in severe adhesion group when compared to mild adhesion group.

Moreover, pregnancy occurring in women after surgical treatment of IUA was associated with a number of obstetric complications, including ectopic pregnancy, cervical incompetence, midtrimester loss, placenta previa, placenta abruption, premature rupture of membrane, placenta accrete syndrome, neonatal death, and stillbirth when compared with general population and this suggests that conceiving after surgical treatment of AS requires increased surveillance during their pregnancy.

Women should be offered an earlier ultrasound examination to verify the location of the pregnancy; the fallopian tube is the most common location of ectopic pregnancy (~95%); however, implantation in the abdomen (<1%), cervix (1%), ovary (1–3%), and caesarean scar (1–3%) can occur [11, 74].

Key Points

1. Lysis of intrauterine adhesions under direct hysteroscopic visualization is generally regarded as the mainstay of treatment for Asherman's syndrome.
2. Hysteroscopic lysis can be done using scissors, monopolar energy systems, bipolar energy systems, or neodymium-doped yttrium aluminum garnet [Nd-YAG] laser.
3. In experienced hands, vaginoscopy—no-speculum hysteroscopy—prevents trauma and can help in severe cases of IUA.
4. Mechanical separation of IUA using scissors is the most accessible means of adhesiolysis.
5. Myometrial scoring technique has been effective for the creation of a uterine cavity in women with severe IUAs having very narrow or obliterated cavity.
6. Assisted or ancillary or guided techniques have been described to improve the safety in difficult and severe occlusive disease.

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