Special Article

AAGL Practice Report: Practice Guidelines for Management of Intrauterine Synechiae

AAGL Advancing Minimally Invasive Gynecology Worldwide

Background

Intrauterine adhesions (IUAs) have been recognized as a cause of secondary amenorrhea since the end of the 19th century [1], and in the mid-20th century, Asherman further described the eponymous condition occurring after pregnancy [2]. The terms "Asherman syndrome" and IUAs are often used interchangeably, although the syndrome requires the constellation of signs and symptoms (in this case, pain, menstrual disturbance, and subfertility in any combination) and the presence of IUAs [2]. The presence of IUAs in the absence of symptoms may be best referred to as asymptomatic IUAs or synechiae.

Identification and Assessment of Evidence

This AAGL Practice Guideline was produced after electronic resources including Medline, PubMed, CINAHL, the Cochrane Library (including the Cochrane Database of Systematic Reviews), Current Contents, and EMBASE were searched for all articles related to IUAs. The MeSH (in MED-LARS) terms included all subheadings, and keywords included Asherman syndrome; Intrauterine adhesions; Intrauterine septum and synechiae; Hysteroscopic lysis of adhesions; Hysteroscopic synechiolysis; Hysteroscopy and adhesion; and Obstetric outcomes following intrauterine surgery.

The search was not restricted to English language literature; committee members fluent in languages other than English reviewed relevant articles and provided the committee with relative information translated into English. Because of the paucity of data in this area, all published works were included for the electronic database searches, and relevant articles not available in electronic sources (e.g., published before the beginning of electronic database commencement) were cross-referenced from hand-searched bibliographies and included in the literature review. When necessary, authors were contacted directly for clarification of points published.

Diagnosis

In women with suspected IUAs, physical examination usually fails to reveal abnormalities [3,4]. Blind transcervical sounding of the uterus may reveal cervical obstruction at or near the level of the internal os [3]. Hysteroscopy has been established as the criterion standard for diagnosis of IUA [5]. Compared with radiologic investigations, and provided the endometrial cavity can be accessed, hysteroscopy more accurately confirms the presence, extent, and morphological characteristics of adhesions and the quality of the endometrium. It provides a real-time view of the cavity, enabling accurate description of location and degree of adhesions, classification, and concurrent treatment of IUAs [6].

Hysterosalpingography (HSG) using contrast dye has a sensitivity of 75% to 81%, specificity of 80%, and positive predictive value of 50% compared with hysteroscopy for diagnosis of IUAs [7,8]. The high false-positive rate (up to 39% [9]) limits its use, and it is does not detect endometrial fibrosis [2]. However, sonohysterography, also called saline infusion sonography, was as effective as HSG in a number of studies, with both reported to have a sensitivity of 75%, and positive predictive value of 43% for sonohysterography or saline infusion sonography and 50% for HSG, compared with hysteroscopy [8,10]. Transvaginal ultrasonography has a sensitivity of 52% and specificity of 11% compared with hysteroscopy [10]. Three dimensional ultrasonography may be

Table 1
Classification of intrauterine adhesions

Source	Summary of classification
March et al [5]	Adhesions classified as minimal, moderate, or severe based on hysteroscopic assessment of the degree of uterine cavity involvement.
Hamou et al [13]	Adhesions classified as isthmic, marginal, central, or severe according to hysteroscopic assessment.
Valle and Sciarra [14]	Adhesions classified as mild, moderate, or severe according to hysteroscopic assessment and extent of occlusion (partial or total) at HSG.
Wamsteker; European Society for Hysteroscopy [15]	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 [16]	Complex scored system of mild, moderate, or severe IUAs based on extent of endometrial cavity obliteration, appearance of adhesions, and patient menstrual characteristics based on hysteroscopic or HSG assessment.
Donnez and Nisolle [17]	Adhesions classified into 6 grades on the basis of location, with postoperative pregnancy rate the primary driver. Hysteroscopy or HSG are used for assessment.
Nasr et al [18]	Complex system creates a prognostic score by incorporating menstrual and obstetric history with IUA findings at hysteroscopic assessment.

HSG, hysterosalpingography; IUA, intrauterine adhesion.

more helpful in the evaluation of IUAs, with sensitivity reported to be 87%, and specificity of 45%, compared with 3-dimensional sonohystography [11]. Magnetic resonance imaging has not been fully evaluated and cannot be recommended until further research is undertaken.

Guidelines for Diagnosis of IUAs

1. Hysteroscopy is the most accurate method for diagnosis of IUAs and should be the investigation of choice when available. Level B.
2. If hysteroscopy is not available, HSG and hysterosonography are reasonable alternatives. Level B.

Classification

Classification of IUAs is useful because the prognosis is related to severity of disease [6]. A number of classification systems have been proposed for Asherman syndrome, each of which includes hysteroscopy to determine the characteristics of adhesions [12]. To date, there are no data from comparative analysis of these classification systems. Table 1 gives the available classification systems and their key features.

Guidelines for Classification of IUAs

1. Intrauterine adhesions should be classified because this is prognostic for fertility outcome. Level B.
2. The various classification systems make comparison between studies difficult to interpret. This may reflect inherent deficiencies in each of the classification systems. Consequently, it is currently not possible to endorse any specific system. Level C.

Management

Because IUAs are not life-threatening, treatment should be considered only when there are signs or symptoms of pain, menstrual dysfunction (including hematometra), infertility, or recurrent pregnancy loss. Surgery is the criterion standard in management of Asherman syndrome, and there is no role for medical treatments. There are no randomized controlled trials (RCTs) of any treatment vs expectant management or any other treatment. The primary objective of intervention is to restore the volume and shape of the uterine cavity to normal and to facilitate communication between the cavity and both the cervical canal and the fallopian tubes. Secondary objectives include treating associated symptoms (including infertility) and preventing recurrence of adhesions.

Expectant Management

The limited data supporting a role for expectant management, published in 1982, demonstrate resumption of menstruation in as many as 78% of patients within 7 years, and pregnancy in 45.5% [19].

Cervical Probing

Cervical stenosis without damage to the uterine cavity or endometrium has been treated using cervical probing with or without ultrasound guidance [20]. All available data were accrued before the advent of hysteroscopically directed adhesiolysis, and uterine perforation has been reported after blind cervical probing. Consequently, this technique currently has a limited role.

Dilation and Curettage

Dilation and curettage was widely used before the widespread use of hysteroscopy, and reported results included return to normal menses in 1049 of 1250 women (84%),

conception in 540 of 1052 women (51%), miscarriages in 142 of 559 pregnancies (25%), term delivery in 306 of 559 pregnancies (55%), premature delivery in 50 of 559 pregnancies (9%), and 42 of 559 pregnancies (9%) complicated by placenta accreta [19]. The severity of adhesions in this group is unknown, though most were likely mild. With the availability of hysteroscopy, dilation and curettage should not be performed because accurate diagnosis and classification are not possible.

Hysteroscopy

Hysteroscopic treatment enables lysis of IUAs under direct vision and with magnification. The uterine distention required for hysteroscopy may itself lyse mild adhesions, and blunt dissection may be performed using only the tip of the hysteroscope [21]. The more lateral the adhesions and the greater their density, the more difficult the dissection and the greater the risk of complications such as perforation [2]. Monopolar [14,22–25] and bipolar [26,27] electrosurgical instruments and the Nd-YAG laser [14,24,28] have been described as techniques used to lyse adhesions under direct vision, with the advantages of precise cutting and good hemostasis. Disadvantages include potential visceral damage if uterine perforation occurs [6], further endometrial damage predisposing to recurrence of IUAs [29,30], cost, and the degree of cervical dilation required to accommodate the operative instruments. None of these techniques has been compared with any other; consequently, there is no available evidence that one method is superior to any other.

Other hysteroscopic techniques

Techniques have been described for the treatment of severe cohesive IUA when typical hysteroscopically directed techniques are not possible or safe. Myometrial scoring has been reported to be effective for creation of a cavity in women with severe IUAs. In this technique, 6 to 8 4-mm deep incisions are created in the myometrium using electrosurgery with a Collins knife electrode from the fundus to the cervix. These incisions enable widening of the uterine cavity. Anatomic success has been reported in 71% in one small series [31], and 51.6% in another [23], with pregnancy achieved in 3 of 7 women (42.9%) and 12 of 31 women (38.7%), respectively.

Additional guiding techniques for hysteroscopy

Fluorscopically-guided blunt dissection of severe adhesions has been described using a hysteroscopically directed Tuohy needle under image intensifier control with the patient under general anesthesia [32]. This technique is costly, exposes the patient to ionizing radiation, and is technically challenging. Its advantages include use of a narrow hysteroscope, reduced risk of uterine perforation, and reduced risk of visceral damage should perforation occur, because no energy source is applied. A similar technique is described in an

ambulatory setting using local anesthesia [33], with described success in mild adhesions only.

Transabdominal ultrasound has been described as a technique to guide hysteroscopic division of IUAs [2,30,31,34,35]. Advantages of the technique include the availability of ultrasound and its noninvasive nature; however, uterine perforation has been reported in as many as 5% of cases [27,31,36]. Laparoscopic guidance is reported to aid hysteroscopically directed division of severe IUAs and enable concurrent inspection of the pelvic organs [27,31,36]. Another approach described for treatment of IUAs with cavity obliteration is the use of a cervical dilator sequentially directed from the cervical canal toward the 2 ostia, creating 2 lateral landmarks and a central fibrous septum, which is then divided transcervically with a hysteroscopic technique under laparoscopic guidance. A small series of 6 women has been reported, with uterine perforation in 2 women and substantial hemorrhage in another [36]. All 6 women had subsequent cavity restoration, with 5 pregnancies achieved by 4 women resulting in 4 live births. Despite the apparently good fertility outcome, with such limited data and high morbidity, this technique cannot be recommended.

Uterine perforation has been reported with this guiding technique; however, recognition and treatment of extrauterine trauma may be of benefit [2,27,31,36]. The increased cost and potential morbidity associated with laparoscopy must be considered.

Nonhysteroscopic Methods of Treating IUAs

Laparotomy, hysterotomy, and subsequent blunt dissection through adhesions using a finger or curette has been a traditional treatment for severe IUAs [3,20,37]. A review of 31 cases and case series treated using this approach reported conception in 16 of 31 women (52%), with live birth in 11 (38%) including 8 (26%) who delivered at term. Of the 16 women who conceived, placenta accreta complicated the pregnancy in 5 (31%) [19]. In contemporary practice, this technique is rarely used and is reserved only for severe cases in which other techniques are not practical or possible [38].

Ancillary Treatments

Physical barriers

Insertion of an intrauterine device (IUD) provides a physical barrier between the uterine walls, separating the endometrial layers after lysis of IUAs [5,19,39]. A class 1 study examined the use of the IUD after hysteroscopic adhesiolysis [39], comparing 2 groups, both of which received an IUD; 1 group underwent early repeat intervention at 1 week and both groups received estrogen or progestin therapy. There was no difference in pregnancy rates or live births. There was no control group. Copper-containing and T-shaped IUDs cannot be recommended because of their inflammatory provoking properties [40] and small surface area [41], respectively. An inert loop IUD (e.g., Lippes loop) is considered the

IUD of choice when treating IUAs [2], although it is no longer available in many geographic areas. In a small nonrandomized study, postoperative IUD plus hormone therapy was compared with hormone therapy alone; no significant difference was found insofar as re-formation of adhesions [42]. The risk of infection when an IUD is introduced into the uterus immediately after adhesiolysis is estimated to be 8% [43], and perforation of the uterus during IUD insertion has been reported [43].

The use of a Foley catheter for 3 to 10 days after surgical lysis of IUAs is similarly reported to act as a physical intrauterine barrier [5,20,33,44–46]. A nonrandomized study compared use of an inflated pediatric Foley catheter in place for 10 days postoperatively in 59 patients with that of an IUD in situ for 3 months in 51 patients [43]. There were fewer infections in the Foley group and a lower recurrence rate of IUAs as assessed using HSG [43]. Although amenorrhea continued in 19% of women in the Foley group and 38% in the IUD group, the fertility rate was relatively low in both groups: 20 of 59 (34%) and 14 of 51 (28%), respectively. In a study of 25 women with moderate to severe IUAs, use of a fresh amnion graft over an inflated Foley catheter prevented recurrence of IUAs in 52% of women, although follow-up fertility data and complications are not reported [46].

A number of newer adhesion barriers are modifications of hyaluronic acid that have been reported to be successful after treatment of IUAs [47–49]. There is one class 1 study of 150 women who underwent suction curettage after incomplete, missed, or recurrent miscarriage [47]. Fifty women were randomized to receive an adhesion barrier (Seprafilm; Genzyme Corp., Cambridge Massachusetts), and 100 patients served as the control group. In the adhesion barrier group, 32 of 32 patients (100%) became pregnant in the 8 months after the procedure compared with 34 of 56 patients (54%) in the control group. Adhesions were found in 1 of 10 women (10%) women receiving treatment compared with 7 of 14 (50%) in the control group who had not become pregnant. No adverse events were reported in the treatment group.

Auto-cross-linked hyaluronic acid gel may also be suitable for preventing IUAs because of high sensitivity and prolonged residency time on an injured surface [50]. In a randomized control trial of 84 women, auto-cross-linked hyaluronic acid gel (Hyalobarrier gel; FAB-Fidia Advanced Polymers, Abano-Terme, Italy) was compared with no therapy after surgical treatment of Asherman syndrome. Postoperative ultrasound studies demonstrated that the walls of the uterine cavity remained separated for at least 72 hours. At second-look hysteroscopy 3 months after the procedure, IUAs were substantially reduced in patients receiving the adhesion barrier compared with the control group (6 of 43 [14%] vs 13 of 41 [32%]; p <.05) [48].

Hormonal Treatments

Postoperative treatment with estrogen therapy (a daily oral dose of 2.5 mg conjugated equine estrogen with or without opposing progestin for 2 or 3 cycles) [12,32,38,51] has been described after surgical treatment of intrauterine adhesions. No comparative studies have been performed investigating dosage, administration, or combination of hormones. One nonrandomized study reported that hormone treatment alone is as effective as hormone treatment and IUD in combination [42].

Techniques to Increase Vascular Flow to Endometrium

Various studies have described use of medications such as aspirin, nitroglycerine, and sildenafil citrate to increase vascular perfusion to the endometrium [52–55] and enable pregnancy [56]. However, the numbers of women treated using these therapies are small, and because all such treatment is off-label, these medications cannot be endorsed outside of rigorous research protocols.

Antibiotic Therapy

There are no data to support the use of antibiotic therapy before, during, or after surgical treatment of Asherman syndrome. The American College of Obstetricians and Gynecologists guidelines for antibiotic use in gynecologic procedures do not recommend their use for diagnostic or therapeutic hysteroscopy [57]. There is, however, a theoretic risk of secondary infection, and it has been proposed that infection may be a primary cause of IUAs. This has led many surgeons to treat patients undergoing surgical lysis because of Asherman syndrome with preoperative or intraoperative antibiotic therapy, and some continue with postoperative antibiotic therapy; however, at this time, there is no evidence to support or refute the use of antibiotic therapy.

Guidelines for Treatment of IUAs

1. It is reasonable to offer expectant management as an alternative to intervention in selected women with IUAs. Level C.
2. There is no evidence to support the use of blind cervical probing. Level C.
3. There is no evidence to support the use of blind dilation and curettage. Level C.
4. Hysteroscopic guidance is the treatment of choice for symptomatic IUAs. Level C.
5. Direct visualization of the uterine cavity at hysteroscopy in conjunction with a tool for adhesiolysis is the treatment of choice for IUAs. Level B.
6. In the presence of extensive or dense adhesions, treatment should be performed by an expert hysteroscopist familiar with at least one of the methods described. Level C.
7. There is no evidence that hysteroscopic adhesiolysis guided by external imaging techniques or laparoscopy prevents uterine perforation or improves clinical outcome; however, such an approach used in appropriately selected patients may minimize the consequences if perforation occurs. Level B.

8. Laparotomy should be reserved as a last line of treatment when hysteroscopic technique is inappropriate or fails to restore intrauterine anatomy. Grade C.

9. Because of the suppressive or inflammatory effect on the endometrium, neither progestin-releasing nor copper or T-shaped IUDs should be used after surgical division of intrauterine adhesions. Grade C.

10. There are limited data supporting a benefit for using a Foley catheter or an IUD after surgical lysis of IUAs. There exists the potential for increased infection rates, and neither technique can be recommended for routine use outside of clinical trials. Grade C.

11. Barriers such as hyaluronic acid and auto-cross-linked hyaluronic acid gel seem to reduce the risk of adhesion recurrence and may be of benefit after treatment of IUAs. At this time, their effect on posttreatment pregnancy rates is unknown, and they should not be used outside of rigorous research protocols. Grade A.

12. Postoperative hormone treatment using estrogen, with or without a progestin, may reduce recurrence of IUAs. Grade B.

13. Medications to improve vascular flow to the endometrium should not be used outside of rigorous research protocols. Grade C.

14. There is no evidence to support or refute the use of preoperative, intraoperative, or postoperative antibiotic therapy in surgical treatment of IUAs. Grade C.

Postoperative Assessment

The recurrence rate is as high as 1 in 3 women with mild to moderate IUAs [14,58,59] and 2 of 3 with severe IUAs [23]. Consequently, regardless of the surgical intervention used, reassessment of the uterine cavity, usually after 2 to 3 cycles after surgery, is worthwhile [23]. Ambulatory methods include office hysteroscopy and HSG, with recurrence of more than mild IUA likely requiring anesthetic and division as described.

Guidelines for Postoperative Assessment After Treatment of IUAs

1. Follow-up assessment of the uterine cavity after treatment of IUAs is recommended. Grade B.

Recommendations for Future Research

There is a paucity of high-quality data in the subject area of IUAs. It is recognized that surgical technique would be difficult to investigate in appropriate research protocols; however, the following considerations are proposed for future research:

1. Randomized trials of intraoperative and postoperative antibiotic therapy for surgical and fertility outcomes.

2. Randomized trials of adjunctive hormone use for surgical and fertility outcomes.

3. Randomized trials of barrier methods (IUD, Foley catheter, and chemical adhesion barriers) for surgical and fertility outcomes.

It is recognized that a universal classification system would be beneficial to future research studies, although given the current limitations of any single classification system, this is unlikely to occur.

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Appendix

Studies were reviewed and evaluated for quality according to the method outlined by the US Preventive Services Task Force:

I. Evidence obtained from at least 1 properly designed, randomized, controlled trial.

II-1. Evidence obtained from well-designed controlled trials without randomization.

II-2. Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than 1 center or research group.

II-3. Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III. Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A. Recommendations are based on good and consistent scientific evidence.

Level B. Recommendations are based on limited or inconsistent scientific evidence.

Level C. Recommendations are based primarily on consensus and expert opinion.