Asherman syndrome—one century later

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Objective: To provide an update on the current knowledge of Asherman syndrome.
Design: Literature review.
Setting: The worldwide reports of this disease.
Patient(s): Patients with Asherman syndrome who presented with amenorrhea or hypomenorrhea, infertility, or recurrent pregnancy loss.
Intervention(s): Hysteroscopy and hysteroscopic surgery have been the gold standard of diagnosis and treatment respectively for this condition.
Main Outcome Measure(s): The etiology, pathology, symptomatology, diagnosis, treatment, and reproductive outcomes were analyzed.
Result(s): This syndrome occurs mainly as a result of trauma to the gravid uterine cavity, which leads to the formation of intrauterine and/or intracervical adhesions. Despite the advances in hysteroscopic surgery, the treatment of moderate to severe Asherman syndrome still presents a challenge. Furthermore, pregnancy after treatment remains high risk with complications including spontaneous abortion, preterm delivery, intrauterine growth restriction, placenta accrete or praevia, or even uterine rupture.
Conclusion(s): The management of moderate to severe disease still poses a challenge, and the prognosis of severe disease remains poor. Close antenatal surveillance and monitoring are necessary for women who conceive after treatment. (Fertil Steril® 2008;89:759–79. ©2008 by American Society for Reproductive Medicine.)

Key Words: Intrauterine adhesion, Asherman syndrome, hysteroscopic adhesiolysis, infertility, synechia, hysteroscopy, amenorrhea

It has been more than a century since Heinrich Fritsch (1) first described a case of posttraumatic intrauterine adhesion. In 1927, Bass (2) reported 20 cases of cervical obstruction in a series of 1500 patients who had undergone induced abortions. In 1946, Stamer (3) reviewed 37 cases reported in the literature and added 24 cases of his own with intrauterine adhesions associated with gravid uterus. In 1948, Joseph G. Asherman published a series of papers (4–7) to describe the frequency, etiology, symptoms, and roentgenologic picture of this condition, and Asherman syndrome has been used to describe the disease ever since. There have been an increasing number of cases of this syndrome described worldwide. The focus of research in the initial 50 to 60 years has been on the prevalence, etiology, and the pathology of this disease. As the understanding of this condition improves, together with the advent of endoscopic technology, the focus of research has now been shifted more toward diagnosis, treatment, and reproductive outcomes. This review provides an update on the current knowledge of the etiology, pathology, symptomatology, diagnosis, treatment, and reproductive outcomes of Asherman syndrome.

Received February 7, 2008; revised and accepted February 7, 2008.
D.Y. has nothing to disclose. Y-M.W. has nothing to disclose. Y.C. has nothing to disclose. E.X. has nothing to disclose. T-C.L. has nothing to disclose.
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DEFINITION

From Asherman's original definition, the syndrome was a consequence of trauma to the endometrium, producing partial or complete obliteration in the uterine cavity and/or the cervical canal, resulting in conditions such as menstrual abnormalities, infertility, and recurrent pregnancy loss.

Although the original description of Asherman syndrome was primarily based on a series of cases of intrauterine adhesions produced after curettage of the gravid uterus, it is now understood that there are several possible underlying causes of intrauterine adhesions. Consequently, the term Asherman syndrome should not be confined to only cases following curettage of the gravid uterus (see the section on etiology).

The term "syndrome" in Greek refers to "concurrence of symptoms," a group of symptoms that collectively indicate or characterize a disease. In this respect, the diagnosis of Asherman syndrome should be made only in women with clinical symptoms. There are cases in whom the formation of intrauterine adhesions is not associated with any clinical symptoms. In these cases, one should avoid using the term "Asherman syndrome" because there are no symptoms at

all; instead, one should use the term "asymptomatic intrauterine adhesions."

Adhesions are composed of fibrotic tissue, which may result in the adherence of opposing surfaces. It is possible that, after injury to the endometrium, fibrosis may follow with the potential for adhesion formation.

Fibrosis without adhesion may represent another spectrum of the same disease. On one end of the spectrum, fibrosis may be mild and superficial. On other end of the spectrum, it may be very severe and involve a large area and extend deep into the myometrium without producing adhesion between two opposing surfaces. The original description of Asherman syndrome referred to intrauterine adhesions, not fibrosis. The question is, should the diagnosis of Asherman syndrome be based on intrauterine adhesion only, or should one include intrauterine fibrosis as well?

The problem with the inclusion of fibrosis is the potentially subjective nature of the diagnosis, especially if the fibrosis involves a small area of the endometrium. Consequently, although we advocate that fibrosis should be included in the diagnostic criteria, it ought to be confirmed by histologic examination of the area concerned to verify the presence of fibrotic tissue. In other words, in our opinion, the diagnosis of Asherman syndrome should be based on:

1. One or more clinical features: amenorrhea, hypomenorrhea, subfertility, recurrent pregnancy loss, or a history related to abnormal placentation including previa and accreta.
2. The presence of intrauterine adhesions by hysteroscopy and/or histologically confirmed intrauterine fibrosis.

Nowadays, as more and more cases of endometrial ablations are performed, it is likely that more and more cases of intrauterine adhesions will be produced after these procedures, with symptoms and hysteroscopic findings similar to Asherman syndrome.

PREVALENCE

The prevalence of Asherman's syndrome varies both by different populations studied as well as by the types of investigation used for diagnosis (Table 1) (8–27). In 1982, Schenker and Margalioth (28) reviewed 90 articles, reporting on a total of 2981 cases of Asherman syndrome in various countries; they found that the incidence was especially high in Israel (770 out of 2981), Greece (456 out of 2981), and South America (445 out of 2981). The prevalence of adhesions varied geographically, and the discrepancies could be explained by several factors: [1] the degree of awareness of the clinicians; [2] the number of therapeutic and illegal abortions in different parts of the world; [3] whether sharp, blunt, or suction curettage is used for puerperal and postabortal evacuation (29); [4] the incidence of genital tuberculosis and puerperal infection in different countries; and [5] the criteria used for diagnosis of intrauterine adhesions.

CLASSIFICATION

To be able to evaluate the extent of the adhesions, determine the most appropriate therapeutic regimen, and predict the results of treatment, a proper classification of the disease is necessary.

Over time, a variety of classifications of the syndrome have been based on different diagnostic tools. According to their findings on hysterosalpingography (HSG), Toaff and Ballas (30) classified intrauterine adhesions into four groups, based on a semiquantitative evaluation. With the advent of hysteroscopy, various investigators have created a series of classifications (31–33) based on the extent of adhesions and the visualization of the ostia. However, none of these classifications took into account the various clinical presentations, especially with regard to the menstrual history.

In 1988, the American Fertility Society developed an objective scoring system for classification of intrauterine adhesions that correlated the menstrual history with hysteroscopic and hysterosalpingographic findings (Table 2) (34). Conversely, the European Society of Hysteroscopy (ESH) and European Society of Gynecological Endoscopy (ESGE) adopted the classification developed at the Hysteroscopy Training Center in the Netherlands by Wamsteker (Table 3) (35). Both of these classification schemes appear to be more thorough, but they are rather complex and difficult to use.

More recently, an improved classification system has been developed that takes into account clinical presentations, hysteroscopic findings, and past reproductive performance (36). This scoring system is attractive because of its potential to predict reproductive outcome.

None of these classification systems have been validated by clinical studies, and no one has used them uniformly when reporting reproductive outcome after treatment of intrauterine adhesions. Thus, comparisons among the different reports that include outcomes is difficult.

ETIOLOGY

Trauma to a Gravid Uterine Cavity

Trauma to a gravid uterine cavity is known to be the main cause of Asherman syndrome. Such trauma could be induced by uterine curettage in the postpartum period (9, 20), after spontaneous miscarriage or during termination of pregnancy (16), or by cesarean section (37). Among the 1856 cases of Asherman syndrome reviewed by Schenker and Margalioth (28), pregnancy was the dominating predisposing factor (1686 out of 1856; 90.8%), with 66.7% (1237 out of 1856) of Asherman syndrome cases occurring after postabortion/miscarriage curettage, 21.5% (400 out of 1856) after postpartum curettage, 2% (38 out of 1856) after cesarean section, and 0.6% (11 out of 1856) after evacuation of a hydatidiform mole.

One of the possible explanations for the gravid uterus being a major predisposing factor to Asherman syndrome is the low estrogen status at the time of the operation or immediately afterward, as the endometrium depends on estrogen for regeneration.

TABLE 1

The prevalence of Asherman syndrome in different populations.

Study	Year of publication	Study type	Characteristics of cases	Number of cases	Number of cases with Asherman syndrome	Comments
Jones (8)	1964	NA	Women with secondary amenorrhea	350	6	NA
			Women following post-partum curettage	78	7	NA
Smid and Bedo (9)	1978	Retrospective	Women following puerperal curettage	69	20	NA
Taylor et al. (10)	1981	NA	Women with otherwise unexplained infertility	235	48	Detected hysteroscopically
Adoni et al. (11)	1982	NA	After curettage for miscarriage	120	18	NA
Stillman and Asarkof (12)	1985	NA	Infertile women	537	26	HSG and/or hysteroscopy
Marty (13)	1986	NA	Women before IUD insertion with normal gynecologic history	351	9	Hysteroscopy
Vutyavanich et al. (14)	1989	Retrospective	Women with secondary amenorrhea	137	7	NA
Golan et al. (15)	1992	NA	Patients after a D&C for a missed miscarriage	60	10	Hysteroscopy
Friedler et al. (16)	1993	Prospective	After only one miscarriage	98	16	Hysteroscopy
			After two miscarriage	21	3	
			After three or more spontaneous miscarriage	28	9	
Raziel et al. (17)	1994	Prospective	Recurrent miscarriages	106	25	Both HSG and diagnostic hysteroscopy
Romer (18)	1994	Prospective	After a dilatation and curettage for incomplete or missed miscarriages	53	16	Hysteroscopy
La Sala et al. (19)	1998	Prospective	Infertile women for whom two IVF-ET cycles failed in which $>$ or $=$2 good-quality embryos were transferred	100	6	Diagnostic hysteroscopy

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TABLE 1

Continued.

Study	Year of publication	Study type	Characteristics of cases	Number of cases	Number of cases with Asherman syndrome	Comments
Westendorp et al. (20)	1998	Prospective	Secondary puerperal procedure for placental remnants or a repeat curettage for incomplete miscarriage	50	20	Hysteroscopy 3 months after the intervention
Tam et al. (21)	2002	Prospective randomized, controlled trial follow-up study	After surgical evacuation of retained products of conception after spontaneous miscarriages	26	2	Hysteroscopy 6 months later
Nawroth et al. (22)	2003	Retrospective	Women with primary infertility	379	26	Diagnostic minihysteroscopy
Preutthipan and Linasmita (23)	2003	Prospective, comparative	Infertile women	336	74	Undergoing both HSG and diagnostic hysteroscopy
Hinckley and Milki (24)	2004	Consecutive	Infertile women scheduled for in vitro fertilization	1000	30	Hysteroscopy
Ventolini et al. (25)	2004	Prospective cohort study	With unexplained recurrent 1st- or 2nd-trimester miscarriages and no live births	23	5	Hysteroscopy
Yucebilgin et al. (26)	2004	Retrospective	Infertile women	115	2	Diagnostic hysteroscopy
Dalton et al. (27)	2006	Case series	After manual vacuum aspiration for the treatment of early pregnancy failure.	262	5	Hysteroscopy

Notes: D&C, dilation and curettage; IVF-ET, in vitro fertilization/embryo transfer; HSG, hysterosalpingogram; IUD, intrauterine device; NA, not applicable.

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TABLE 2

The American Fertility Society classification of intrauterine adhesions, 1988.

Extent of Cavity Involved	<I/3	1/3–2/3	>2/3
	1	2	4
Type of Adhesions	Filmy	Filmy & Dense	Dense
	1	2	4
Menstrual Pattern	Normal	Hypomenorrhea	Amenorrhea
	0	2	4

Prognostic classification		HSG[a] score	Hysteroscopy score
Stage I	(Mild)	1-4	
Stage II	(Moderate)	5-8	
Stage III	(Severe)	9-12	

Source: The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, mullerian anomalies and intrauterine adhesions. Fertil Steril 1988;49:944-55. (34)

[a] All adhesions should be considered dense.

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Another possible explanation could be the physiologic changes that occur in a gravid uterus around the pregnancy period. The uterus could be in a vulnerable state after pregnancy, making the basal layer of endometrium more easily damaged by any trauma, especially curettage. Westendorp et al. (20) reported that, with ambulatory hysteroscopy, intrauterine adhesions were found in 40% of the women undergoing either a secondary removal of placental remnants after delivery or a repeat curettage for incomplete abortions.

Trauma to Nongravid Endometrium

Trauma to a nongravid uterine cavity could also result in Asherman syndrome. Schenker and Margalioth (28) reported that Asherman syndrome may follow a diagnostic curettage (30 out of 1856, 1.6%), abdominal myomectomy (24 out of 1856, 1.3%), cervical biopsy or polylectomy (10 out of 1856, 0.5%), insertion of an intrauterine device (3 out of 1856, 0.2%), or the use of radium (1 out of 1856, 0.05%). The development of intrauterine adhesions can also result from various forms of hysteroscopic surgery. In a prospective, randomized study on 95 women who underwent hysteroscopic surgery, Taskin et al. (38) found that the frequency of Asherman syndrome was 6.7% (1 out of 15) of patients after resection of septa, and 31.3% (10 out of 32) and 45.5% (9 out of 20) of patients after hysteroscopic resection of solitary fibroids and multiple fibroids, respectively. More recently, one case of intrauterine adhesion was found after bilateral uterine artery embolization (UAE) (39); another was found after uterine devascularization because of severe postpartum hemorrhage (40).

Endometrial ablation is often followed by the formation of intrauterine adhesions. The incidence of adhesion formation in women treated with thermal balloon ablation was reported to be 36.4% (41). This is not surprising because the basal layer of the endometrium is often removed or destroyed, ostensibly creating a local environment that is either nonconducive to, or insufficient for, regeneration of the endometrium, followed by the subsequent replacement of the luminal epithelial lining of the uterine cavity with fibrosis. There have been reports on the formation of intrauterine adhesions after various forms of endometrial ablation (41–43).

Infection

There has been some controversy over the exact mechanism whereby infection could result in Asherman syndrome. Several investigators (10, 44, 45) maintained that the primary cause of intrauterine adhesions has been infection, especially chronic or subacute endometritis; others (18, 46) have held the opposite view, based on a study by Polishuk et al. (47) of 171 women who had undergone cesarean sections. Among these 171 cases, 28 patients developed significant endometritis. Afterward, HSG showed no difference in the occurrence of intrauterine adhesions between endometritis group and the control group (no infection). They concluded that endometritis is unlikely to be a major factor in the pathogenesis of intrauterine or endocervical adhesion. Nevertheless, some investigators (48, 49) believe that inflammatory processes do contribute to the damaging effect of trauma and act synergistically to produce intrauterine adhesions. Uterine trauma and subsequent inflammation, in conjunction with a low estrogen status, may potentially lead to fibrosis.

Since the first report in 1956 (50), it has been recognized that endometrial tuberculosis may result in severe intrauterine adhesions, often with total obliteration of the uterine

TABLE 3

European Society of Gynecological Endoscopy (ESGE) classification of IUAs (1995 version).

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

Source: Wamsteker, 1997, Hysteroscopy Training Centre, Spaarne Hospital, Haarlem, The Netherlands. (35)

[a] From findings at hysteroscopy and hysterography.

[b] Only to be classified during hysteroscopic treatment.

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cavity and total destruction of the endometrium with resulting amenorrhea and infertility. Among the 1856 cases of Asherman syndrome reviewed by Schenker and Margalioth (28), genital tuberculosis was found in 74 cases (4%).

Congenital Anomaly of the Uterus

In 1985, Stillman and Asarkof (12) carried out a study on infertile couples and found a significant association between Asherman syndrome and Müllerian duct malformations, especially with a septate uterus. Among the 43 infertile patients with Müllerian duct malformations, seven patients (16%) had Asherman syndrome. It is uncertain whether the malformation itself predisposed the women to adhesion formation. It is possible, however, that women with congenital uterine anomalies are at increased risk of recurrent pregnancy loss. In consequence, they may have repeated surgical evacuation of the uterus that then increases the chances of adhesion formation in the uterus.

Genetic Predisposition

In addition to the above predisposing factors, there may be an individual constitutional element, as some patients have apparently developed a severe form of intrauterine adhesions after a gentle suction curettage procedure (51), or for no apparent reason.

PATHOLOGY

Histologically, Asherman syndrome is a condition in which the endometrium becomes fibrosed (52). The endometrial stroma is largely replaced by fibrous tissue, and the glands are usually represented by an inactive cubo-columnar epithelium of the endometrial type. The distinction between the functional and basal layer of the endometrium is lost, and the functional layer is replaced by an epithelial monolayer, which is nonresponsive to hormone stimulation and fibrous synechiae forms across the cavity. In other cases, there may be calcification or even ossification in the stroma, and the glands may be sparse and inactive or cystically dilated. Vascularity might be abundant, containing thin-walled dilated vessels, but in most cases the tissue become avascular.

Adhesions may involve different layers of the endometrium, myometrium, or connective tissue. Adhesions derived from each of these tissues exhibit a characteristic hysteroscopic picture: endometrial adhesions are quite similar in appearance compared with the surrounding endometrium. Myofibrous

adhesions, which are most often encountered, are characterized by the presence of a thin layer of overlying endometrium, the surface of which is furnished with many glandular ostia. The surface of connective tissue adhesions lack an endometrial lining and contrast markedly with the adjacent endometrium. Fibrous adhesions that show dense connective tissue exhibit no lining in contrast to surrounding endometrium (53).

Using full-thickness myometrial biopsy specimens of patients, Yaffe et al. (54) reported that the uterine wall contained 50% to 80% of fibrous tissue compared with 13% to 20% of the control group. March (55) postulated that fibrosis limits uterine myometrial activity and reduces the perfusion of sex steroids, resulting in atrophy. Sometimes fibrosis involving the basal layers of the endometrium or the myometrium may occur without detectable intrauterine adhesions.

The extent of the endometrial damage may not directly correlate with the severity of the symptoms. For obstructive amenorrhea, the lesion is often focal and limited to the uterine isthmus and cervical canal. A biopsy of the fundal part of the uterine cavity often reveals normal or inactive endometrium.

The histologic appearance after transcervical resection of the endometrium (TCRE) is similar to that of Asherman syndrome (56). However, in addition to the fibrosis, other changes may be detrimental, including epithelioid or foreign body granuloma, collections of hemosiderin, black-brown carbon, and metallic pigment (56, 57), or less commonly, necrotizing granulomatous inflammation (58).

SYMPTOMATOLOGY

The symptoms of Asherman syndrome include menstrual abnormalities, infertility, recurrent pregnancy loss, and other pregnancy complications.

Menstrual Abnormalities

Menstrual abnormalities, including hypomenorrhea and amenorrhea, remain the most common clinical features (1339 out of 1973, 68%) (28) associated with Asherman syndrome. Amenorrhea may be caused by various etiologic factors: [1] cervical adhesions blocking menstrual flow; [2] severe endometrial fibrosis leading to destruction of the entire basal layer of the endometrium (59). Dysmenorrhea is occasionally present (55 out of 1973, 3.5%) (28). In atretic amenorrhea, mechanical obstruction of the internal cervical os could lead to secondary amenorrhea, periodic discomfort or pain, hematometra, and even hematosalpinx.

Infertility

Schenker and Margalioth (28) analyzed the symptoms of 2151 cases of Asherman syndrome. They found that infertility was present in 43% of women studied (802 out of 2151). One possible reason for infertility is the occlusion of the tubal ostia, uterine cavity, or the cervical canal caused by adhesions. These synechiae could prevent the migration of sperm or implantation of the embryo.

Repeated Pregnancy Loss

Although a severe degree of intrauterine adhesions causes obstruction of the cavity and infertility, a milder degree of adhesions may be associated with repeated pregnancy loss. The possible etiologic factors for recurrent pregnancy loss include: [1] constriction of the uterine cavity caused by adhesions; [2] lack of a sufficient amount of normal endometrial tissue to support implantation and development of the placenta; and [3] defective vascularization of the residual endometrial tissue consequent upon fibrosis of endometrium (60).

Other Pregnancy Complications

The spontaneous conception rate with Asherman syndrome was reported as 45.5% (133 out of 292) (28). It was further reported by Schenker and Margalioth (28) that, among 165 pregnancies in women with untreated Asherman syndrome, the rate of spontaneous miscarriage was 40% (66 out of 165), preterm delivery was 23% (38 out of 165), term delivery was 30% (50 out of 165), placenta accrete was 13% (21 out of 165), and ectopic pregnancy was 12% (2 out of 165). The pregnancy complication rates in this group of patients appeared to be high, although there was no proper control group.

Theoretically, the defective placentation also may lead to intrauterine growth restriction (IUGR), though there have been only several cases of IUGR described in pregnant women with Asherman syndrome after endometrial ablations (61). The defective uterine endometrium and obliterated uterine cavity may also predispose women to ectopic tubal and cervical pregnancies (62–64). There has never been any report on fetal limb amputation associated with Asherman syndrome, although limb amputation is associated with the presence of amniotic bands after amniocentesis.

Endometrial Ablation

Endometrial ablation could lead to intrauterine adhesions, and those patients who conceived would be expected to develop pregnancy complications not dissimilar to those of Asherman syndrome resulting from other reasons. In a recent literature review of 70 pregnancies after endometrial ablations, Hare and Olah (61) found the following complications in 70 postablation pregnancies: ectopic pregnancy (1 out of 70, 1.4%), spontaneous miscarriage (15 out of 70, 21%), premature delivery (13 out of 70, 18.6%), IUGR (3 out of 70, 4%), and morbidly adherent placenta (10 out of 70, 14.3%). In this study, there were only four normal pregnancies reported (4 out of 70, 5.7%). In 2005, Mukul and Linn (42) reported a case of significant fetal malformations, including positional deformities in the neck, an asymmetric chest, severe scoliosis, and limb abnormalities, associated with uterine synechiae resulting from previous endometrial ablation. In a retrospective study of 39 pregnancies after transcervical resection of endometrium (TCRE) with cutting loop, Xia et al. (65) observed five ectopic pregnancies (12.8%); 32 cases with intrauterine pregnancy were terminated under ultrasound guidance with two difficult procedures. Only one

pregnancy resulted in spontaneous miscarriage, which was managed by suction curettage. One term pregnancy had placenta increta, resulting in a caesarean hysterectomy.

Endometrial Malignancy

In patients with intrauterine adhesions severe enough to produce amenorrhea, the remaining biologically active endometrium, in however small an amount, might undergo malignant change, and the diagnosis in such a situation could potentially be very difficult. Sandridge et al. (66) first reported a case of endometrial carcinoma in a 71-year-old woman who developed postmenopausal bleeding while receiving unopposed estrogen. Hysteroscopic examination showed extensive intrauterine synechiae and a polypoid lesion adjacent to an adhesion band. Biopsy of the polypoid lesion confirmed endometrial adenocarcinoma. They concluded that Asherman syndrome and endometrial adenocarcinoma can exist simultaneously. In such cases, hysteroscopy is essential for target biopsy.

Clinical–Pathological Correlation

The clinical features are closely associated with pathologic findings, such as the depth of fibrosis, location of the adhesions, and extent of the pathologic changes. The location of the adhesion can include the cervical canal, uterine cavity, or both cervical canal and uterine cavity (Fig. 1).

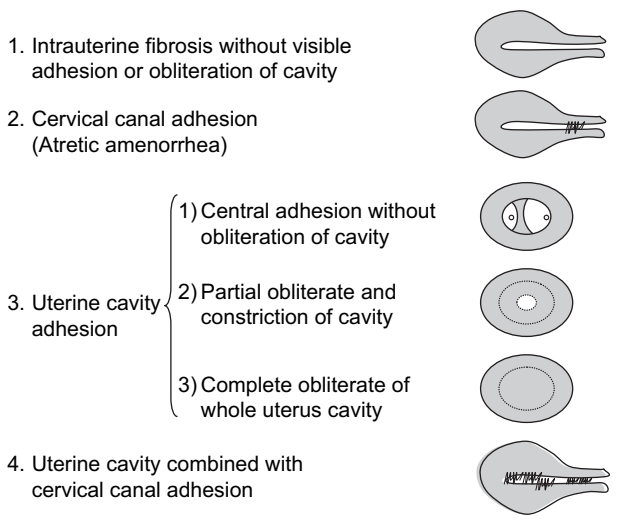
Obstructive amenorrhea is a consequence of intracervical adhesions or stenosis, and patients often present with amenorrhea with periodic abdominal discomfort. There may be a normal uterine cavity and a good prognosis after treatment.

Frequently, the adhesions are in the uterine cavity. It is the most common category and has several subcategories, which we characterize as central intrauterine adhesion without constriction of the cavity, partial obliteration of the cavity with constriction, and complete obliteration of the cavity. In all of these conditions, the patient may present with any symptoms described in previous section, and the extent of disease can be confirmed by hysteroscopy. The extent of the disease will influence the prognosis after treatment. Patients with central intrauterine adhesions always have some normal endometrium and a relatively normal cavity. Therefore, the prognosis after treatment is usually good. Patients with partial obliteration of the cavity have a reduced and irregular cavity, and no cavity can be found in patients with complete obliteration of the cavity. Amenorrhea and infertility are the two most common accompanying clinical features in patients with partial or complete obliterated cavity. The prognosis for pregnancy in these patients is often poor.

In some cases, the adhesions can be located in both cervical canal and cavity of the uterus. The patient may present with any symptoms, including menstrual abnormalities, infertility, and pregnancy complications, and the prognosis (such as normal menses and fertility) depends very much on the severity and extent of the adhesions.

FIGURE 1

Clinical pathology correlation of Asherman syndrome.



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INVESTIGATIONS

The following investigations may be considered in women with suspected Asherman syndrome.

Radiologic Diagnosis

Hysterosalpingography Before the invention of the hysteroscope, HSG was the first-line investigation to visualize the uterine cavity. Today, many gynecologists still consider it to be a valid initial test for Asherman syndrome. Hysterosalpingography has the advantages of being able to outline the areas of occlusion or special filling defects and providing an appraisal of the cornual region, tubal contours, and tubal patency. Wamsteker (67) described the HSG appearance of intrauterine adhesions as defects that appear as sharply outlined intrauterine structures, which are centrally and/or marginally located. These filling defects are often irregular, angulated, and of homogenous opacity. In more severe cases, partial obliteration of the cavity may be observed; its borders may be irregular, and either one or both of the tubes may be occluded. In severe intrauterine adhesions, the uterine cavity is completely distorted and narrowed, and both tubes may be occluded. With complete occlusion of the lower part of the uterine cavity, HSG will fail to show any contrast filling of the uterine cavity and will provide no information on the extent of the adhesions. A short cannula should be used to prevent perforation in cases of suspected severe adhesions.

Several studies have examined the value of HSG in the diagnosis of intrauterine adhesions. In a retrospective study of 400 patients (68), HSG was found to be as accurate as hysteroscopy in diagnosis of normal and abnormal uterine cavities, although the nature of the intrauterine filling defects was accurately revealed by hysteroscopy only. Another

investigation showed that more than one third (38.3%) of HSG examinations may have false-positive findings (17). In a prospective study reported by Soares et al. (69), the diagnostic accuracy of HSG in the detection of intrauterine adhesion was compared with hysteroscopic findings as the gold standard. Among 65 women studied, five had hysteroscopic evidence of intrauterine adhesions; HSG had a sensitivity of 75% in the detection of intrauterine adhesions and a positive predictive value of 50%.

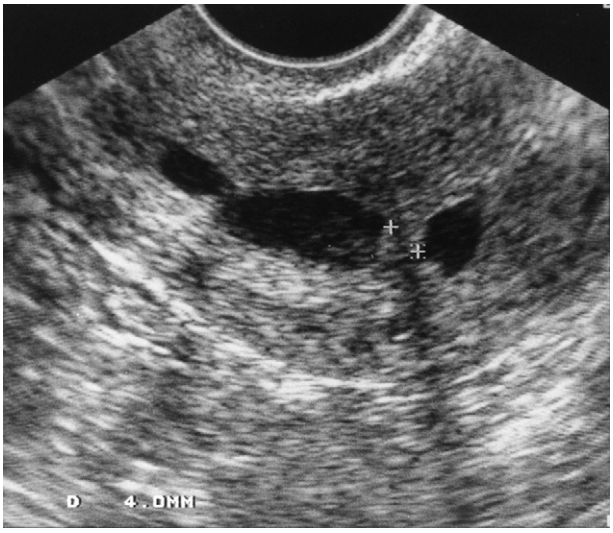
Hysterosalpingography is a simple screening method for intrauterine adhesions, and it remains an important screening procedure for the diagnosis of intrauterine adhesions, especially in the infertile patients because additional information about the fallopian tubes may be obtained. However, HSG has a number of limitations. First, it may not detect endometrial fibrosis per se, as in cases without adhesions. Second, HSG has a high rate of false-positive results and has limitations in defining the nature of identified intrauterine filling defects. Third, minor filmy adhesions might not consistently produce abnormal shadows on HSG. Fourth, air bubbles, mucous, and debris may all mimic filling defects, and poor placement of the cannula can cause intravasation. An excessive amount of contrast medium in the uterus also can obliterate shadows caused by intrauterine adhesions.

Ultrasonography Ultrasonography was used in the diagnosis of endometrial fibrosis or intrauterine adhesion by Confino et al. (70) and Schlaff and Hurst (71). It is a noninvasive procedure that allows visualization of the uterine cavity, which may not otherwise be possible during HSG or hysteroscopy when the uterine cavity has been obliterated. Typically, adhesions appear as dense echoes within the cavity. In women with severe intrauterine adhesions, ultrasonography may show the following typical appearance: the endometrial echo becomes difficult to visualize, with irregular thickness and one or more interruptions of the endometrium at the sites of fibrosis. In addition, there may sometimes be one or more echolucent (cystic-like) areas interrupting the endometrium, representing localized collection of menstrual blood in an area where the functional layers of the endometrium are preserved (Fig. 2).

Both the sensitivity and the specificity of ultrasound in diagnosis of the intrauterine adhesions have been reported to be quite low: the sensitivity of transvaginal ultrasonography was reported as 52% (72) and the specificity as only 11% (73). Nevertheless, ultrasonography is useful when HSG is not possible because of obliteration of lower uterine cavity. In this situation, ultrasonography may be used to evaluate the upper uterine cavity, and the findings maybe of prognostic significance. Schlaff and Hurst (71) used transvaginal ultrasonography to study the endometrial echo in seven patients with Asherman syndrome presenting with amenorrhea and complete obstruction of the uterine cavity before hysteroscopic surgery. They found that patients with normal-appearing endometrium above the level of obstruction are likely to benefit successful hysteroscopic treatment and can expect to resume normal postoperative menstrual function. Patients who have little or no endometrium seen on transvaginal ultrasonography are extremely unlikely to profit by hysteroscopic creation of a uterine cavity from within the myometrium.

FIGURE 2

Transvaginal ultrasonography of a case of Asherman syndrome with typical interrupted endometrial echo. There were several hyperechoic bridges indicating intrauterine adhesions, with several echolucent areas in between the bridges indicating collection of menstrual blood in areas where there are functioning endometrial tissues. +, indicates the uterine adhesions.



Yu. Asherman syndrome. Fertil Steril 2008.

Three-dimensional ultrasonography techniques have been used by a few investigators (73, 74) to detect adhesions in the uterine cavity, with a specificity of 45% (73). In the study reported by Soares et al. (69), transvaginal ultrasonography did not detect any of the cases of intrauterine adhesions and yielded three false-positive diagnoses of this disease (sensitivity and positive predictive value of 0).

Sonohysterography Sonohysterography (SHG), which combines transvaginal sonography with intrauterine injection of isotonic saline, has been shown to be as accurate as HSG and to be superior to transvaginal ultrasonography in the detection of intrauterine adhesions (72). In this technique, 20 to 30 mL of saline may be introduced into the uterine cavity through a catheter. Intrauterine adhesions are suspected if there are one or more echogenic areas between the anterior and posterior walls in the liquid-filled uterine cavity, or if the full distension of the cavity was impeded by tethering of the walls by thin or thick bands of synechiae (72). In a study of 19 patients with intrauterine adhesions, the sensitivities of HSG and SHG in the diagnosis of intrauterine adhesions were both 100%, and the sensitivity of transvaginal ultrasonography was only 52% (72). In another study on diagnostic accuracy in 65 infertile women, SHG had both similar sensitivity (75%) and specificity (positive predictive values as 42.9%) to HSG (69).

With SHG, it is possible to perform a complete ultrasound examination of the uterine structure including the uterine cavity and myometrium. However, like HSG, SHG is of value only in cases of partial intrauterine adhesions because normal saline will not be able to enter into the uterine cavity when it is completely obstructed (75, 76). Sonohysterography is useful in situations where transvaginal ultrasonography yields normal results but the clinical suspicion of intrauterine adhesions remains high.

Magnetic resonance imaging Magnetic resonance imaging (MRI) has been used as a tool to investigate patients with Asherman syndrome (77, 78), especially those with involvement of the cervical canal (79). The main advantage of MRI is its ability to image the uterine cavity above the adhesions and assess the endometrial remnants in the upper part of the uterine cavity, which may influence the decision and outcome of treatment. However, the MRI-signal characteristics of intrauterine adhesions have not been examined in detail; it is anticipated that adhesions would produce low signal intensity on T2 images (79). Thus, MRI may have a supplementary role in the diagnosis of complete obliteration of uterine cavity or cervical obstruction that cannot be visualized by hysteroscopy.

Hysteroscopy

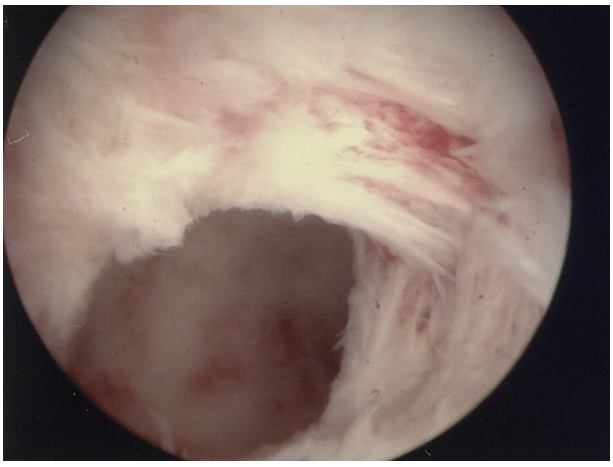
Hysteroscopy, as compared with radiologic tests, can more accurately confirm the presence, extent, and degree of adhesions and the quality of the endometrium because the uterine cavity can be directly inspected. The hysteroscope may be guided through the endocervix under visual control or by ultrasound guidance until the internal os is completely visible or the adhesive obstruction is identified (67).

Al-Inany (80) described the different varieties of intrauterine adhesions as visualized via the hysteroscope: [1] the central adhesion appears as a column with broadening ends connecting the opposite uterine walls; [2] marginal adhesion (which may be easily missed) appears like a crescent or half-drawn curtain, which can hide a cornu or side wall and create an asymmetric aspect to the uterine cavity (Fig. 3), and [3] complex marginal central scars, which divide the uterine cavity into several smaller chambers, can appear, some of which maybe concealed to visual examination. Superficial mucosal adhesions usually have the same color as the surrounding endometrium and can be easily broken down by the pressure of the hysteroscope; the fibrous or myometrial bands appear white in color, and are often dense and difficult to divide. The diagnosis of adhesion resulting from tuberculosis may be suggested by the appearance of a network of small alveoli coating the uterine walls. The fundus may look like a honeycomb. Endometrial fibrosis appears as pale patches on hysteroscopy (81).

If it is not possible to perform a hysteroscopy satisfactorily because of significant obliteration of the cavity, the other alternative diagnostic modalities such as ultrasonography or MRI should be considered. Alternatively, hysteroscopic evaluation may be facilitated by adhesiolysis under ultrasound or other methods of guidance. The methylene blue test may be used to differentiate between fibrosis and normal endometrial lining (32). When methylene blue is injected through the inflow channel of the hysteroscope, the endometrium stains well but connective (fibrotic) tissue and myometrium do not.

FIGURE 3

Hysteroscopic view of a case of Asherman syndrome with adhesions bands in the anterior and left lateral side wall of the uterine cavity.



Yu. Asherman syndrome. Fertil Steril 2008.

TREATMENT

Treatment of Asherman syndrome aims at restoring the size and shape of the uterine cavity, preventing recurrence of the adhesion, promoting the repair and regeneration of the destroyed endometrium, and restoring normal reproductive functions. Over the last century, many surgical techniques have been described.

Expectant Management

Schenker and Margalioth (28) gathered 23 amenorrheic women from the literature who had not undergone any surgical intervention, of whom 18 regained regular menses after 1 to 7 years. For fertility outcome, 292 women in whom treatment was withheld were collated, among whom 133 women (45.5%) conceived spontaneously.

Blind Dilation and Curettage

Before the advent of hysteroscopy, Asherman syndrome was treated by dilation and curettage of the uterus. It is not surprising that this method resulted in a high incidence of uterine perforation and had a low success rate. This method is now considered obsolete.

Hysterotomy

Transfundal separation of the walls of endometrial cavity by hysterotomy has been described. In an analysis of 31 cases of

hysterotomies compiled from a total of 12 reports (28), 16 of 31 cases (52%) conceived and 8 (25.8%) had term deliveries. An additional 3 cases were reported (82), all of which were associated with successful restoration. Two of the women conceived and had live births. This procedure is seldom performed nowadays except in very severe cases where the uterine cavity is completely obliterated.

This technique was employed by Reddy and Rock (83) in three patients who had had previous unsuccessful hysteroscopic resection of intrauterine adhesions. In each case, complete uterine cavity obliteration was noted during hysteroscopy, which was terminated and converted to exploratory laparotomy. To delineate the borders of the cavity, a uterine sound was placed in the cavity transcervically to identify the internal os clearly. For demarcation of the cornual areas obliterated completely by scar, a 2.0 nylon suture was threaded through the fimbria to pass through into the uterus. All three of the patients resumed normal menstruation after surgical treatment, with reestablishment of the uterine cavity and regeneration of the endometrium. Postoperative HSG results in all three patients revealed residual endometrial scarring. Two of these patients required further hysteroscopic lysis of mild adhesions. The investigators concluded that this technique showed promising results in reestablishing the integrity of the uterine cavity in cases of complete obliteration where there are no landmarks in the uterine cavity to guide the surgeons in separating the cavity walls. However, longer-term follow-up assessments in a large number of patients are required to verify the value of this technique.

Clearly, this method of treatment should only be considered in the most extreme of situations, and patients should have been counseled with regard to the complications of a laparotomy, the potential risk of bleeding with hysterectomy, and the risk of scar rupture during subsequent pregnancies.

Hysteroscopic Adhesiolysis

Hysteroscopic surgery is now the treatment of choice for Asherman syndrome because of its minimally invasive nature and also because it can be performed under direct vision. Adhesiolysis usually begins inferiorly and can be advanced cephalically until the uterine architecture has been normalized (80). Sometimes, the mere touch of the endoscope can be sufficient to separate filmy columns of adhesions. In most cases, adhesiolysis may be performed with the help of the hysteroscopic scissors or other cutting modalities such as laser or diathermy. In general, filmy and central adhesions should be divided first as these are more easily distinguished; marginal and dense adhesions are more difficult to identify, and division of these adhesions carries an increased risk of uterine perforation.

Hysteroscopic adhesiolysis using scissors or biopsy forceps (84, 85) has the advantage that it permits dissection and avoids complications related to energy sources, and it possibly minimizes the destruction of endometrium. Surgery that uses energy sources either with the electrode or laser vaporization system could provide effective and precise cutting as well as good hemostasis, but there is a theoretical possibility of further endometrial damage (86, 87). Electrosurgery systems, such as a monopolar cutting needle, Versapoint bipolar have been used in treatment of intrauterine adhesions (88–91).

If thermal energy is used to divide the adhesions, the minimal amount of energy must be used to avoid further damage of endometrial tissue. Thermal damage of endometrium may be limited by using an electrode needle rather than a cutting loop because of the reduced exposure to the current. Several studies have reported successful outcomes of adhesiolysis by using electrosurgery, which suggests that with proper application significant damage is unlikely (92–94). Cararach et al. (94) demonstrated that there was no difference in outcome between the use of scissors and resectoscope. On the other hand, electrosurgery achieves better hemostasis compared with the use of scissors, thus providing an improved optical clarity of the operative field.

Surgery using laser vaporization, including Nd-YAG laser and KTP laser, have been reported by Newton et al. (95) and Chapman and Chapman (96). The depth of necrosis in the latter modality has been described as minimal, at about 1 to 2 mm.

Operative hysteroscope in outpatient setting with CO_2 distension also has been used (16, 87), but the method is limited only to those patients with filmy intrauterine adhesions. At present, this method is rarely used for hysteroscopic adhesiolysis.

Methods of guidance Hysteroscopic division of intrauterine adhesions may be technically difficult, especially if the adhesions are dense. It carries a significant risk of perforation of uterus, especially during the dilatation of the cervical channel and introduction of the hysteroscope. The introduction of the dilator and hysteroscope must be guided carefully by one of the methods described here to avoid perforation because perforation at this early stage would preclude satisfactory completion of the hysteroscopy. The efficiency and safety of hysteroscopic surgery for Asherman syndrome may be improved if the procedure is guided by one of the following methods.

Laparoscopy Laparoscopy is a commonly used method for monitoring hysteroscopic adhesiolysis. Some investigators have performed hysteroscopic surgery under concomitant laparoscopic control to prevent perforation of the uterus (32, 88, 94). This is of particular importance if the adhesions are dense. Lateral perforation of the uterus may cause significant bleeding, compared with central perforations. When the uterine wall becomes unduly thin, it will permit transmission of light across the uterine wall, and there will be a bulge over the remaining serosal layer, which signifies that further hysteroscopic surgery must immediately stop. However, with laparoscopic guidance, it is often too late to prevent the perforation. Nevertheless, it has the advantage of detecting the

perforation immediately, preventing any further trauma to pelvic organs. Laparoscopy may also provide an opportunity to inspect the pelvis, to diagnose and treat any concurrent pathology such as endometriosis or adhesions.

Fluoroscopic control Broome and Vancaillie (97) described a fluoroscopically guided hysteroscopic division of adhesions for an obliterated uterine cavity where several isolated pockets were located near the fundus. A 16-gauge, 80-mm Tuohy needle was introduced into the endocervical canal alongside a 5-mm diagnostic hysteroscope. Ultravist 76.9% was injected through the needle under fluoroscopic and hysteroscopic control. A passageway to hidden pockets of endometrium was created using the needle located radiographically, and subsequent division of adhesions was performed under direct vision with hysteroscopic scissors. This technique provides an intraoperative fluoroscopic view of pockets of endometrium behind an otherwise blind-ending endocervical canal in women with severe Asherman syndrome.

Gynecoradiologic uterine resection (GUR) One group (98, 99) reported the use of a special catheter inserted into the cavity through the cervix with a balloon attached to its tip. Radio-opaque dye was injected through a side channel of the catheter to delineate the uterine cavity with its adhesions, and hysteroscopic scissors were introduced through a central channel of the catheter to divide the adhesions. In 13 patients (9 mild, 3 moderate, and 1 severe adhesions), the adhesions were lysed successfully in 81.2%. In four cases (two moderate and two severe), lysis of adhesions was only partially successful. These procedures had to be abandoned prematurely because of patient discomfort (n = 1), visualization difficulty (n = 1), and thick, fibrotic adhesions that were resistant to scissors (n = 2). This was described as an ambulatory technique resulting in minimal discomfort; however, the effectiveness of this procedure needs to be further evaluated as the study consisted of a small sample size (n = 17). The disadvantage of this method relates to radiation exposure.

Transabdominal ultrasound guidance Transabdominal ultrasound guidance has been increasingly used to replace laparoscopic guidance during hysteroscopic division of intrauterine adhesions, especially in women with severe intrauterine adhesions. When there are severe adhesions in the uterine cavity, it may be very difficult to identify the cavity without ultrasound. Our opinion is that transabdominal ultrasonography provides efficient monitoring of the hysteroscopic procedure and guiding the scope toward the uterine cavity even when the adhesions may have completely or almost completely obliterated the uterine cavity. It can significantly decrease the risk of perforation of uterus, especially during the procedure of dilatation of cervical channel. Moreover, it is a nontraumatic, readily available technique.

Other Techniques

Several other innovative surgical techniques have been described for women with severe adhesions.

Transcervical adhesiolysis after the use of laminaria tent Chen et al. (88) described the use of a laminaria tent and transcervical adhesiolysis in their small series of seven patients. The laminaria tent was used to distend the short, narrow, scarred cervical cavity, thus facilitating the insertion of the transcervical resectoscope. Initially one or two of the tents were inserted into the cervix and left in situ with a vaginal pack for 24 hours. At the end of this time, the tents were replaced with three to four new tents, which were now placed within the uterine cavity itself and were removed 24 hours later. Gentle and gradual dilation of the cervical canal ensued as the laminaria absorbed fluid and gradually swelled after insertion. Hysteroscopic lysis of intrauterine adhesions was then performed under general anesthesia with a continuous flow resectoscope. Simultaneous laparoscopy was used to guide the surgery. No intraoperative complications were recorded among the small number of women who participated in the study (n = 7). All their patients achieved normal menstruation after treatment, and a normal uterine cavity was demonstrated on repeat HSG/hysteroscopy.

Pressure lavage under guidance (PLUG) Coccia et al. (100) developed a technique based on sonohysterography in which a continuous intrauterine injection of saline solution led to mechanical disruption of intrauterine adhesions. In that report, five patients with mild adhesions obtained satisfactory lysis of the adhesions and restoration of menses. However, two patients with moderate adhesions underwent repeated treatment by hysteroscopy several months after the procedure because of the reformation of filmy adhesions. One out of the seven patients in the study achieved a pregnancy. This technique may be more suitable for patients with mild adhesions.

Conversion of a "blind" hysteroscopic procedure to a "septum" division McComb and Wagner (101) used a variant hysteroscopic technique in six patients with severe intrauterine adhesions. The indication in all the cases was lack of communication between the cornua and the cervical canal as shown by HSG. This method was performed hysteroscopically with concomitant laparoscopic guidance. A 5-mm hysteroscope was introduced with fluid used as the distending medium. A Pratt cervical dilator (gauge 13F) was passed through the cervix with the curved tip pointing laterally toward the uterine cornu. The dilator was aligned with the plane of the uterine corpus. The limit of passage was determined by the bulging of the cornua as seen by laparoscopy. This maneuver was performed bilaterally for a completely obliterated cavity. Thus, bilateral passage of the cervical dilator converted the obliterated uterine cavity into the configuration of a uterine "septum." The scar was cut with hysteroscopic scissors in side-to-side swaths, from one lateral passage to the other, until the fundus was reached and the uterine cavity had been liberated.

In all six patients, regular menstruation was restored. Five women achieved conception, of whom four had live births. Three perforations and one hemorrhage were encountered among the six women. All the perforations were central. Postoperative HSG showed that the uterine cavity was within

normal limits in four patients. One patient had residual intrauterine adhesion necessitating another hysteroscopy.

Myometrial scoring technique Protopapas et al. (102) and Capella-Allouc et al. (103) reported a myometrial scoring technique for treatment of severe Asherman syndrome associated with the presence of dense intrauterine adhesions and marked reduction in the size of the uterine cavity. This technique aims to restore the normal size and shape of the uterine cavity and uncover functional endometrium by making six to eight 4-mm deep longitudinal incisions into the myometrium with two or three lateral incisions from the fundus to the isthmus on both sides and two or three transverse incisions at the fundus. The procedure stops at that point even if the ostia are not visible. The surgery is monitored by either concomitant laparoscopy or abdominal ultrasound scan. At the end of the surgery, the cervix is dilated up to Hegar 12–18 to reduce the likelihood for postoperative cervical stenosis. in Their small series of seven patients, Protopapas et al. (102) found that four needed a repeat procedure. The usefulness of this method remains to be seen.

Repeat Surgery

Because of the possibility of recurrence of adhesions, all patients undergoing surgery for intrauterine endometrial adhesions or endometrial fibrosis must be counseled regarding the possibility of a repeat surgery (85). This is especially true if the adhesions are of severe degree (32). In general, patients with severe intrauterine adhesions often require several repeated procedures because of the difficult nature of the procedure and the high rate of reformation of adhesions.

Genital Tuberculosis

There have been only a few reports on hysteroscopic lysis of intrauterine synechiae secondary to genital tuberculosis. In a study of 12 consecutive patients with total synechiae due to tuberculosis, three perforations (20%) occurred during 15 attempts at hysteroscopic adhesiolysis, and reformation of the adhesion occurred in all patients (104). Pabuccu et al. (89) reported that, of 25 women with severe Asherman syndrome, two women had genital tuberculosis, and both had recurrence of intrauterine adhesions. In another report by Preutthipan and Linasmita (90), among 65 patients who had surgery for Asherman syndrome, two had recurrence, and both had genital tuberculosis. Therefore, Bukulmez et al. (104) concluded that total uterine synechiae due to tuberculosis, unlike other conditions, carries a poor prognosis after hysteroscopic lysis. Surrogacy may be the only remaining option for fertility when all other surgical attempts have failed.

Complications during Procedures

Complications during the adhesiolysis procedure include perforation of the uterus, hemorrhage, and pelvic infection (Table 4). Uterine perforation occurred in about 2% (10 out of 592) of all cases reported. However, the rate was up to 9% (17 out of 188) in those with severe adhesions. The incidence of perforation can be reduced by ultrasound guidance (106, 107). Hemorrhage is a less commonly reported; however, it is unclear whether hemorrhage is a less common occurrence or whether it is underreported by various studies.

Prevention of Recurrence of Adhesion

Because of the high rate of reformation of intrauterine adhesions (3.1% to 23.5%), especially severe adhesions (20% to 62.5%) (Table 5), prevention of reformation of adhesions after surgery is essential to successful treatment. Various methods have been used to achieve this aim.

Intrauterine contraceptive devices The insertion of an intrauterine device (IUD) has been advocated by many studies as an effective, widely used method to prevent adhesion reformation (28, 108–110). Postoperative use of an IUD keeps the raw, dissected surfaces separated during the initial healing phase and may reduce the chances that they will readhere to one another (111). Originally, an IUD was used to lyse and prevent intrauterine adhesions by Polishuk and Kohane (112).

Over the last two decades of IUD use, a number of studies have been performed with various types. In a prospective

TABLE 4

Complications of hysteroscopic adhesiolysis for Asherman syndrome.

Study	Year of publication	Complications	All cases	Severe cases
Valle and Sciarra (32)	1988	Perforation	5/187 (2.7%)	3/47 (6.4%)
Pistofidis et al. (105)	1996	Hemorrhage	5/86 (5.8%)	3/11 (27.3%)
Pabuccu et al. (89)	1997	Perforation	1/40 (2.5%)	1/10 (10%)
McComb and Wagner (101)	1997	Perforation	—	3/6 (50%)
		Hemorrhage	—	1/6 (16.7%)
Broome and Vancaillie (97)	1999	Perforation	—	2/55 (3.6%)
Feng et al. (85)	1999	Perforation	4/365 (1.1%)	4/39 (10.3%)
Capella-Allouc et al. (103)	1999	Perforation	—	4/31 (12.9%)

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TABLE 5

Outcome of hysteroscopic adhesiolysis for Asherman syndrome: restoration of menstruation in women presenting with amenorrhea or hypomenorrhea.

Study	Year of publication	Normal menses following surgery, number (%)	Reformation of intrauterine adhesions	Reformation of intrauterine adhesions in severe cases
Fedele et al. (84)	1986	11/21 (52.4%)	—	—
Valle and Sciarra (32)	1988	149/169 (88.2%)	44/187 (23.5%)	23/47 (48.9%)
Pabuccu et al. (89)	1997	29/34 (85.3%)	8/40 (20%)	6/10 (60%)
Feng et al. (85)	1999	294/351 (83.8%)	—	—
Capella-Allouc et al. (103)	1999	—	—	10/16 (62.5%)
Preutthipan and Linasmita (90)	2000	45/50 (85%)	2[a]/65 (3.1%)	2[a]/10 (20%)

[a] Both of the patients who had reformation had tuberculosis of the genital tract.

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observational study by Vesce et al. (113), 48 women with functional secondary amenorrhea were treated with the insertion of a copper IUD. Forty patients had the regular menses within a few weeks after insertion of the device. The investigators attributed this effect to the inflammatory reaction stimulated by copper IUDs in the endometrium as a consequence of the release of various types of prostaglandins and enzymes. In a literature review, March (111) discussed the use of IUDs and concluded that T-shaped IUDs may have too small a surface area to prevent adhesion reformation, and that IUDs containing copper may induce an excessive inflammatory reaction. Therefore, their use is not advised in patients who have had intrauterine adhesions. The loop IUD is considered the best choice for the prevention of reformation of intrauterine adhesions (49, 111), although it is no longer available in many countries including the United States.

Up to now, there have been no randomized, controlled trials to confirm the usefulness of IUDs in preventing adhesion reformation after hysteroscopic lysis of intrauterine adhesions. The introduction of an IUD also may carry a small risk of perforation of the uterus.

Foley balloon catheter Some studies have reported on the use of a Foley catheter introduced into the uterine cavity with an inflated balloon for several days after lysis of adhesions to prevent recurrence (51, 114). In 2003, Orhue et al. (115) assessed the use of an IUD or a Foley catheter balloon as an adjunctive treatment of intrauterine adhesion in patients presenting with infertility. In a 4-year initial period, patients with intrauterine adhesion were treated with the insertion of an IUD for 3 months after adhesiolysis (n = 51). In the next 4 years, a pediatric Foley catheter balloon was used for 10 days after adhesiolysis instead of the IUD. In the Foley catheter group (n = 59), 81.4% of the patients had restoration of normal menstruation compared with 62.7% in the IUD group ($P<.05$). Investigation by HSG showed that the need for repeated treatment was also significantly less in the Foley catheter group. The conception rate in the Foley group was 33.9% compared with 22.5% in the IUD group. They concluded that the Foley catheter was a safer, more effective method for preventing reformation of intrauterine adhesions after adhesiolysis.

In a prospective controlled study, Amer et al. (116) assessed the efficacy of an intrauterine balloon in preventing intrauterine adhesions after operative hysteroscopy. A 10F Foley catheter balloon, inflated with 3.5 mL of saline and its stem cut above the cervix, was left intrauterine in 32 patients. The balloon was removed 1 week after the operation. Diagnostic hysteroscopies were performed 6 to 8 weeks postoperatively to evaluate intrauterine adhesions in the group. Intrauterine adhesions were found in seven patients in the group with the balloon (7 out of 32; 21.9%) versus nine patients in the group without a balloon (9 out of 18; 50%) ($P=.04$). After hysteroscopic adhesiolysis, the reformation of intrauterine adhesions was found in four patients in the balloon group (4 out of 12 = 33.3%) versus four patients without the balloon (5 out of 8 = 62.5%) ($P=.199$). These results are of clinical and practical importance although they did not reach statistical significance in subgroup with intrauterine adhesions. The investigators concluded that intrauterine balloon application after operative hysteroscopy is of great value in preventing intrauterine adhesions.

Amer and Abd-EI-Maeboud (117) had tried amnion grafts after hysteroscopic lysis of intrauterine adhesions. In a pilot study involving 25 patients with moderate or severe intrauterine adhesions, hysteroscopic adhesiolysis was followed by intrauterine application of a fresh amnion graft over an inflated Foley catheter balloon for 2 weeks. Second-look hysteroscopy revealed adhesion reformation in 48% of the patients who had had initial severe adhesions, but all had minimal adhesions. Randomized comparative studies are needed to validate this method's benefits, including the reproductive outcomes.

The use of a balloon to prevent adhesion formation after adhesiolysis maintains the freshly separated uterine cavity by separating the opposing uterine walls. However, inserting a Foley catheter balloon and keeping its stem from coming

out of the cervix invites ascending infection from the vagina. The overinflated balloon increases pressure on the uterine walls, which may result in decreased blood flow to uterine walls with potential effects on endometrial regeneration. In addition, this method can produce significant discomfort for the patient.

Hyaluronic acid (HA) Recently, several investigators (118–120) have studied intrauterine application of modified hyaluronic acid (HA). Hyaluronic acid, a natural component of the extracellular matrix, the vitreous humor, and synovial fluid of the joint, has been proposed as a barrier agent to prevent adhesion development after abdominal and pelvic surgery (121). The anti-adhesive effects depend on the preparation's molecular weight as well as its concentration (122). The modified HA, including Seprafilm (Genzyme Corporation, Cambridge, MA) and auto-cross-linked HA (ACP) gel (Hyalobarrier gel; Baxter, Pisa, Italy), has been used to reduce the intrauterine adhesions after adhesiolysis.

Seprafilm, a bioresorbable membrane formulated from chemically modified HA (sodium hyaluronate) and carboxymethyl cellulose, has been shown to significantly reduce intrauterine adhesions. Tsapanos et al. (118) reported on a randomized, controlled trial to evaluate the safety and efficacy of Seprafilm in preventing and reducing postoperative endometrial synechiae formation after suction evacuation or curettage for incomplete, missed, and recurrent abortion. A standard commercial slide of Seprafilm membrane was cut into two pieces. Each piece was rolled into a thin cylinder. After dilation and suction evacuation, the first cylinder was pushed into the endometrial cavity; the second cylinder was detained in the endocervical canal, covering the exo-orifices and endo-orifices. Hysterosalpingography was performed in patients who were still not pregnant 8 months after the intervention to evaluate the results of the study. Seprafilm turns into a hydrophilic gel approximately 24 hours after placement and provides a protective coating around traumatized tissues for up to 7 days during re-epithelization. In the Seprafilm-treated group, only one patient (1 out of 10; 10%) developed intrauterine adhesions; in the control group, seven patients (7 out of 14; 50%) developed intrauterine adhesions.

Auto-cross-linked HA (ACP) is obtained from modified HA and seems particularly suitable for preventing adhesion formation because of its higher adhesivity and more prolonged residence time on the injured surface compared with unmodified HA (123). In a prospective randomized, controlled study (119), ACP gel (Hyalobarrier gel; Baxter) was introduced into the uterine cavity at the end of adhesiolysis procedure in 43 patients with Asherman syndrome. The procedure was considered complete when, under hysteroscopic view, the gel appeared to completely fill the cavity from tubal ostia to internal os. Ultrasonographic data showed that ACP gel was able to keep uterine walls separated for at least 72 hours. With second-look hysteroscopy at the end of the 3-month follow-up period, a statistically significantly lower rate of postsurgical intrauterine adhesions was observed in the group using ACP treatment (6 out of 43) in comparison with the control group (13 out of 41) (14.0% versus 31.7%; $P<.05$).

Hormone treatment Wood and Pena (124) proposed the use of estrogens to stimulate the regeneration of endometrium and promote reepithelialization of the scarred surfaces (125). In a randomized study of 60 women who underwent dilation and curettage (D&C) during the first trimester of pregnancy (125), women who received estrogen–progestin therapy (n = 30) after adhesiolysis had statistically significantly greater endometrial thickness (0.84 cm vs. 0.67 cm; $P=.02$) and endometrial volume (3.85 cm^2 vs. 1.97 cm^2) than the control group (n = 30). These findings suggest that estrogen–progestin therapy does significantly increase endometrial thickness and volume. However, there has been no objective evidence based on randomized, controlled trials to confirm the efficacy of estrogen treatment on the reduction of reformation of intrauterine adhesions.

Many gynecologists do use estrogen therapy after lysis of intrauterine adhesions, but its use has not been universally adopted. In Beijing and Sheffield, we use estradiol valerate, 4 mg/day for 4 weeks, with the addition of a progestogen (e.g., medroxyprogesterone acetate at a dose of 10 mg/day) in the last 2 weeks of the estrogen treatment.

Prevention of Asherman Syndrome

Prevention is always better than cure. To prevent the formation of endometrial fibrosis and adhesions, it is essential that any trauma to the uterus be avoided, especially in the pregnant or postpartum state.

1. Avoid postpartum or postabortion curettage Diagnosis of retained products of conception would present a clinical challenge. Although ultrasonographic examination may be potentially useful, its accuracy has not yet been established. Saline infusion sonohysterography has enhanced our ability to diagnose retained products of conception (126). Alcazar (127) tried transvaginal B-mode ultrasonography combined with color velocity imaging and pulsed Doppler to detect retained trophoblastic tissue and concluded that this investigation could be useful to detect retained trophoblastic tissue and to select patients suitable for conservative management. Transvaginal duplex Doppler ultrasonography is also an effective noninvasive method for evaluating patients with persistent postpartum hemorrhage (128).

Curettage in the postpartum or postabortion period should be avoided as far as possible.

Hysteroscopy should be considered an effective method for diagnosis and treatment of retained products of conception. Goldenberg et al. (129) used operative hysteroscopy with a cutting loop working as a curette for selective removal of the adherent residual tissue while avoiding interference with the rest of the endometrial surface. They found that selective curettage of residual trophoblastic tissue directed by hysteroscopy is an easy, short procedure that may be preferable to conventional, nonselective, blind curettage.

2. Perform gentle curettage If surgical evacuation is indeed required in the puerperium or after miscarriage, suction evacuation of the uterus should be undertaken by a senior obstetrician. It should be performed gently, with the use of either suction or a blunt (not sharp) curette to avoid unnecessary trauma.

3. Select medical management of miscarriages When termination of early pregnancy is necessary, medical treatment should be considered instead of surgical options. In a randomized controlled trial of 82 women who had been treated with conservative management, medical means, or surgical evacuation after spontaneous miscarriage, Tam et al. (21) found two cases (2 out of 26; 7.7%) of intrauterine adhesions detected in those managed by surgical evacuation. However, there were no cases of adhesions in patients managed conservatively or by medical means. Earlier regimens assessed the systemic and intrauterine injection of prostaglandins. In a large randomized, multicenter study supported by WHO that compared intramuscularly administered prostaglandin E_2 (PGE_2) analogue and vacuum aspiration in women with an early pregnancy up to 51 days (130), the overall frequency of complete abortion was 91% for prostaglandin treatment and 94% for vacuum aspirations. This was followed by the introduction of the antiprogestogen mifepristone in combination with prostaglandin (misoprostol) (131–133).

Since its introduction, the uptake of medical abortion has been steadily increasing in countries where it has been available for routine use. In a prospective, randomized, placebo-controlled trial, Tang et al. (134) compared the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks' gestation and found that the combination of mifepristone and misoprostol is effective for medical abortion up to 63 days. Both sublingual and vaginal are effective routes of administration.

Similarly, in the management of incomplete miscarriage or delayed miscarriage, expectant or medical treatment should be considered (135).

Outcomes of Treatment

Surgical success may be judged by the restoration of normal anatomy in the uterine cavity. The rate of successful anatomic restoration of a first procedure has been reported to range from 57.8% to 97.5% (136, 137). However, even when the uterine cavity has been restored anatomically, the extent of endometrial fibrosis will determine the reproductive outcome. Hence, the restoration of both uterine anatomy and the function of the endometrium are equally important.

Adhesion reformation has been a major limiting step to the success of the operation. The reformation of intrauterine adhesions appears to be directly related to the severity of the adhesions. It has been reported that the recurrence rate for intrauterine adhesions ranges from 3.1% to 23.5% among all cases of intrauterine adhesions and from 20% to 62.5% in those with severe adhesions (Table 5). Repeated surgery for those who have adhesion reformation may be worthwhile as there have been case reports of conception and delivery after repeated surgical adhesiolysis (101–103).

Another measure of the success of the procedure is restoration of normal menses. The return of menstruation has been reported to range from 52.4% to 88.2% (Table 5). From five available studies, we can conclude that, of 625 women who underwent surgical treatment of Asherman syndrome, 528 (84.5%) regained normal menstruation.

Finally, in women who present with infertility or pregnancy wastage, the outcome may be measured in terms of pregnancy rate and live birth rate. Pace et al. (137) reported that, in women with Asherman syndrome, pregnancy rate varied from 28.7% before surgery to 53.6% after hysteroscopic treatment. In a study of women with two or more previous unsuccessful pregnancies (136), the operative success as measured by live birth rate improved from 18.3% preoperatively to 68.6% postoperatively. In the literature (summarized in Table 6), the pregnancy rate after hysteroscopic lysis of intrauterine adhesions in women who wanted to have a child has been about 74% (468 out of 632), which is much higher than found in untreated women (46%). The pregnancy rate after treatment in women with infertility is about 45.6% (104 out of 228); the successful pregnancy rate after treatment in severe cases is reported to be consistently lower (18 out of 55 = 33%). For women with previous pregnancy wastage, both the pregnancy rate and the live birth rate after treatment are reasonably high (121 out of 135 = 89.6% and 104 out of 135 = 77.0%, respectively).

PROGNOSIS

Before the use of hysteroscopy, the pregnancy rate after treatment was reported to be 51% (540 out of 1052), which was only slightly better than found in those who had not been treated (133 out of 292; 46%) (28). Women with Asherman syndrome who underwent hysteroscopic division of adhesion had increased rates of conception (468 out of 632; 74%). Among those who conceived, the live birth per pregnancy achieved was 529 out of 666 (79.4%; see Table 6). Women who conceive after treatment of Asherman syndrome still have a high risk of pregnancy complications, including spontaneous abortion, premature delivery, abnormal placentation, intrauterine growth restriction (IUGR), and uterine rupture during pregnancy or delivery.

Everett (140) reported that, in the general population, in 550 women who conceived, bleeding occurred before the 20th week in 117 patients (117 out of 550; 21%), and 67 pregnancies (67 out of 550; 12%) ended in miscarriage. The spontaneous miscarriage rate after treatment of intrauterine adhesions was around 20% (94 out of 477) (see Table 6). It is unclear whether this represents an increase in the risk of early miscarriage after treatment of Asherman syndrome, as the likelihood of miscarriage in the general population (about 15% to 20%) is rather close to this figure.

TABLE 6

Reproductive outcome of hysteroscopic adhesiolysis for Asherman syndrome.

			All cases						Severe cases
Study	Publication year	Characteristics of patients	Number	Conception	Spontaneous pregnancy loss rate	Live birth rate[a]	Premature delivery	Abnormal placenta[b]	Number
Sugimoto (138)	1978	—	—	79	29/29 (36.7%)	45/79 (57.0%)	—	10	—
Fedele et al. (84)	1986	—	—	22	10/22 (45%)	9/22 (40.7%)	—	—	—
Friedman et al.(82)	1986	—	—	24	1/24 (4.2%)	23/24 (95.8%)	—	2	
Valle and Sciarra (32)	1988	Infertility	81	48 (59.2%)	17/48 (35.4%)	29/48 (60.4%)	—	1	30
		Pregnancy loss	106	95 (89.6%)	9/95 (9.5%)	85/95 (89.5%)	—		17
Parent et al. (139)	1988	Wishing to have a child	169	107 (63.3%)	—	91/107 (85.0%)	—	—	73
Pistofidis et al. (105)	1996	Infertility	86[d]	30 (34.9%)	—	21[c]/30 (70%)	—	—	11
Roge et al. (87)	1997	Wishing to have a child	50	28 (56%)	10/28 (35.7%)	24/28 (85.7%)	—	—	—
Pabuccu et al. (89)	1997	Infertility	16	10 (62%)	—	6/10 (60%)	—	—	4
		Recurrent (≥3) miscarriage	24	24 (100%)	—	17/24 (70.8%)	—	—	—
McComb and Wagner (101)	1997	—	—	—	1/6 (16.7%)	5/6 (83.3%)	2/5 (40%)	2	—
Protopapas et al. (102)	1998	—	—	—	1/4 (25%)	2/4 (50%)	1/2 (50%)	—	—
Feng et al. (85)	1999	Wishing to have a child	186	156 (83.9%)	11/156 (7.1%)	145/156 (92.9%)	—	4	—
Capella-Allouc et al. (103)	1999	Wishing to have a child	—	—	5/15 (33.3%)	9/15 (60%)	4/9 (44.4%)	2	28
Preutthipan and Linasmita (90)	2000	Infertility	45	16 (35.6%)	—	16/16 (100%)	—	—	10
		Pregnancy loss	5[d]	2 (40%)	—	2/2 (100%)	—	—	—
Zikopoulos et al. (91)	2004	—	—	—	—	—	10/20 (50%)	—	—
Total				468/632 (74%)[e]		529/666 (79.4%)[f]			

[a] Live birth rate is defined live birth/pregnancy achieved.
[b] Defined as placenta accrete, placenta increta, placenta praevia, retained placenta, and uterine sacculation over the placenta site.
[c] Number of patients delivering a live birth or having a continuing pregnancy.
[d] All patients received in vitro fertilization.
[e] Refers to the total of series for whom the number of cases was reported.
[f] Refers to the total of series for whom the number of conceptions was reported.

Yu. Asherman syndrome. Fertil Steril 2008.

Continued collection of data is required to determine if the miscarriage rate after treatment of Asherman syndrome is increased. This increased rate could be related to the presence of fibrosed endometrium, which impairs successful implantation. Premature delivery has also been reported to be more common in women with Asherman syndrome (see Table 6). Pregnancies after hysteroscopic lysis of adhesions for Asherman syndrome may also be complicated by placenta accreta (111) and placenta increta (85). Other complications, such as retained placenta (85) and uterine sacculation over the placenta site (82), have also been reported. Yasmin and Adeghe (141) reported a case of severe early-onset IUGR at 29 weeks' pregnancy after hysteroscopic adhesiolysis; IUGR may be a consequence suboptimal placentation and hence compromised placenta perfusion during pregnancy. Uterine rupture has been described after hysteroscopic surgery for Asherman syndrome, and it is undoubtedly related to the weakened and scarred uterine wall after surgery (142–146), especially if perforation of the uterus was sustained during the procedure (147, 148).

Thus, pregnancies in women with a history of Asherman syndrome should be considered to be high risk. Careful monitoring during the antenatal period, especially the third trimester, should be undertaken.

CONCLUSION

Asherman syndrome is a worldwide disease. One century after the condition was first reported, a lot of progress has been made in the investigation and treatment of the condition. Hysteroscopy has been the method of choice in the investigation and treatment of the condition. The management of moderate to severe disease still poses a challenge, and the prognosis of severe disease remains poor. Repeat surgery may be necessary in some cases but may not always produce the desired outcome. In those who succeed in achieving pregnancy after treatment of the condition, careful surveillance of the pregnancy is essential because a number of obstetrics complications may occur. Future research should focus on the cellular and molecular aspects of endometrial tissue regeneration as well as the prevention of postsurgical adhesion formation and reformation.

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