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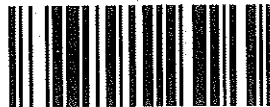
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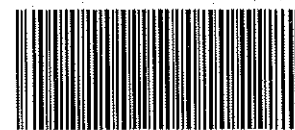
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Intrauterine Adhesions

Jay M. Berman, M.D., F.A.C.O.G.¹

ABSTRACT

Joseph Asherman first described intrauterine adhesions in 1948. It is commonly referred to as Asherman's syndrome and intrauterine synechiae. It is characterized by a spectrum ranging from amenorrhea to menstrual disturbance to normal menses. It is frequently associated with infertility. The true incidence is unknown. Most cases occur within close temporal proximity to a pregnancy, usually within 4 months and usually while the woman is in a hypogestrogenized state. Most cases are associated with trauma to the endometrium from surgical procedures, primarily curettage. Increasingly, cases are associated with myomectomy both abdominal and hysteroscopic, removal of septae, and any other intrauterine surgery. Pathology shows fibrous connective tissue bands with or without glandular tissue, although this may range from filmy to dense.

The diagnosis is primarily by history and a high index of suspicion. Confirmatory tests are increasingly saline infusion hystero-graphy (SIS) or hysterosalpingogram (HSG), although magnetic resonance imaging has also been used. Ultimately, hysteroscopy is employed for the final diagnosis and treatment. Hysteroscopic lysis of adhesions is the main method of treatment. Dense scar tissue and difficult entry into the cervix may require laparoscopic or ultrasound guidance. Most authors use an intrauterine stent and follow treatment with sequential estrogen and progesterone therapy. Increasingly early intervention either with repeat SIS or HSG or most recently with flexible hysteroscopy has been advocated.

Treatments outcomes are difficult to assess as there are no universally agreed upon classification system. However, intrauterine pregnancies rates range from 22 to 45% and live births range from 28 to 32%. The risk of complications for those that achieve pregnancy is significant with a significant risk for placenta accreta and subsequent blood loss, transfusion, and hysterectomy. Prospective controlled studies are needed to determine the best diagnostic and treatments for intrauterine adhesions.

KEYWORDS: Intrauterine adhesions (IUAs), intrauterine synechiae (IUS), Asherman's syndrome

The condition we now commonly refer to as Asherman's syndrome has been called uterine atresia, amenorrhea traumatica, and endometrial sclerosis.¹ This condition has also been referred to as intrauterine adhesions (IUAs) and intrauterine synechiae (IUS). The true incidence is unknown but is likely more

common than previously expected. In one series, Dmowski and Greenblatt² found an incidence of 1.55% of women subjected to hysteroscopy.

Joseph G. Asherman first described 29 cases of "amenorrhea traumatica (atretica)" in the *Journal of Obstetrics and Gynecology of the British Empire* (now

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BJOG) in 1948.³ These 29 cases describe a complete obliteration of the endometrial cavity. Amenorrhea ranged from 3 months to 12 years. Eleven of the 29 patients previously had a postpartum hemorrhage, 15 a spontaneous abortion, two a procured (termination) abortion, and one a hydatidiform mole. He also states that therapy for this condition should be surgical not hormonal. Sounding and dilatation of the cervix were the only methods used, and he reported only one perforation. Subsequently, 12 of 29 had normal menstruation, and nine of 29 had hypomenorrhea.³ All together, it was a remarkable case series for 1948.

Indeed, the article further describes the pregnancy outcomes in 10 cases in 3 years. Two were ongoing, three missed abortion, and one intrauterine fetal demise (IUFD) at 8 months. One normal birth required manual removal of the placenta, and one required cesarean section. In all, a record not unlike our current problems with what has become known as Asherman's syndrome. At the conclusion of the article, he makes reference to several articles and abstracts also addressing this as a series of case reports, although he and Stamer disagreed as to the mechanism.³ Asherman makes reference to Stamer's statement that the "menstrual flow continues undisturbed behind the blockage" leading to hematometra. He notes that none of Stamer's cases had hematometria.³ Asherman notes that this condition was reported by Fritsch and others from 1894 to 1933 and that Stamer added 24 of his own cases to the total in 1946.³

In 1950, Asherman followed his original article with a description of "traumatic intrauterine adhesions." He calls this "regional obliteration of the uterine cavity," and he describes it as due the "partial conglutination" of the uterine walls. In amenorrhea traumatica, the cervix and internal os are involved, whereas in intrauterine adhesions it is the endometrial walls. This required the use of x-rays, which show the filling defects. This paper is accompanied by beautifully reproduced hysterosalpingograms of filling defects. Asherman also describes the difficulty of distinguishing polyps, septa, and submucous fibroids. Again, treatment is described as surgical and unlike amenorrhea traumatica, best done at hysterotomy with the finger. He does describe the use of a catheter passed from above into the vagina and removed in 3 days. He noted that the vaginal approach can also be performed but there is risk of perforation. Asherman addresses what was a very difficult problem by suggesting that a strip of gauze saturated with penicillin be left in place for 1 to 2 days. He suggests that with this prophylaxis, it may be possible to eradicate adhesions completely, in contrast with re-formation of the intrauterine adhesions after lysis. In a remarkable prescient statement, he wonders if the operation can be performed by means of hysteroscopy, a possibility still to be investigated in 1950.⁴ Together, these two conditions described by Asherman comprise the clinical spectrum of

what is now usually referred to as Asherman's syndrome.^{3,4} Most of the initial cases were associated with spontaneous abortion, puerperal hemorrhage treated with curettage, and induced abortion. Additionally, infectious causes of Asherman's syndrome have been attributed to schistosomiasis⁵ and tuberculosis.⁶ Depending on the location, these organisms may play an important role in the etiology of intrauterine synechiae, however they do not appear to be common etiologic agents for most patients in the United States. In addition to pregnancy-related trauma, intrauterine surgery has become more important as a cause of this condition.

The true incidence of Asherman's syndrome is unknown as the clinical spectrum ranges from amenorrhea to menstrual disturbance to infertility. The American Society for Reproductive Medicine (ASRM) Practice Committee educational bulletin published in 2006 estimates a frequency of 7% of secondary amenorrhea.⁷

ETIOLOGY

All of the causes of Asherman's syndrome share a common mechanism that involves injury to the pars basalis of the endometrium, usually but not exclusively in close temporal proximity to a pregnancy including postpartum hemorrhage. The increase in intrauterine surgery for myomas, septae, and bicornuate uteri in recent years adds another group of patients susceptible to IUS.

Three types of pathology are present: multiple adhesions between the walls of the uterine cavity, dense adhesions that involve the myometrium, and a sclerotic thin endometrium without adhesions.⁸ The latter patients have the worst prognosis for treatment and subsequent return of menses and fertility.

Whereas the general association with infection is postulated, no consistent findings of infection have been noted.⁹ Despite the lack of association with clinical infections presenting as fever, leukocytosis, and foul-smelling discharge, at least two organisms are clearly associated with IUAs. Krolkowski et al⁵ described in a case report of an African woman with 6 years of amenorrhea after an uncomplicated cesarean delivery. In the course of workup, a small uterine cavity was found obliterated by adhesions. Unfortunately, no follow-up is offered as to the final outcome for this patient. On the other hand, Sharma et al⁶ reported a retrospective series of 28 patients positive for tuberculosis by genital culture or histopathology. These patients presented with a variety of symptoms including oligomenorrhea and amenorrhea as well as primary or secondary infertility. Clearly, since schistosomiasis is not found in the United States and the latest incidence of tuberculosis is 4.6 per 100,000 population, these are not the most common causes of IUAs in the United States.¹⁰

Endometrial ablation, first successfully performed by Goldrath¹¹ in 1981 with the Nd:YAG laser, has led to more than 25 years of procedures and several devices to intentionally reproduce what has been incorrectly called Asherman's syndrome but is in fact usually obliteration of the endometrium without residual synechiae.¹¹ Long-term follow-up of many of these endometrial ablation patients has shown us that not all patients with successful treatments have IUAs.

PATHOLOGY

The findings of Asherman's syndrome vary considerably from complete obliteration to minimal adhesions. There can also be filmy, fluffy adhesions or dense adhesions that are difficult to cut with hysteroscopic scissors. The extent of findings at hysteroscopy includes adhesion of the cavity ranging from filmy to severe, total atresia, and cervicoisthmic adhesions. Adhesions in the cavity are the most common, whereas total atresia and cervicoisthmic adhesions are rare.¹² The histologic appearance is variable and can be endometrial, myometrial, or connective tissue. Most frequent are fibromuscular bands, sometimes lined with endometrium.² Endometrium obtained by curettage at the time of treatment of adhesions was secretory in 80%, proliferative in 12%, atrophic in 5%, and hyperplastic in 3%.^{12,13} It appears that dense fibrous adhesions without glands carry the worst prognosis for patients in terms of both menses and fertility and present the greatest difficulty in treatment.

DIAGNOSIS

Suspicion of Asherman's syndrome is the most important criterion for diagnosis of this entity. Patients may present with only mild menstrual disturbances after abortion, postpartum hemorrhage, or intrauterine surgical procedures. Others may have relatively normal menstrual cycles and only present with complaints of infertility. Of course, other causes of amenorrhea and menstrual disturbances should be ruled out. Pregnancy is the most frequent cause of amenorrhea in this age group and should be assessed prior to any other workup. Secondary amenorrhea of course is associated with many causes including polycystic ovarian syndrome, hypothalamic amenorrhea, ovarian failure, and hyperprolactinemia. Asherman's syndrome should be considered in any patient with a recent history of trauma to the uterine cavity. Laboratory evaluation should consist of serum pregnancy test, complete blood count, and, depending on the history and physical examination, follicle-stimulating hormone, thyroid stimulating hormone (TSH), and prolactin.⁷ In almost all cases of IUAs, the physical examination will be normal.

Patients who are treated with estrogen and progesterone in sequence may have a variable response to

treatment. Depending on the dose and length of therapy and extent of disease, patients may have no bleeding or light or normal withdrawal bleeding.

In any event, clinical suspicion is most important, and patients with a compatible history should have imaging of the endometrial cavity to establish the diagnosis. Hysteroscopy was mentioned by Asherman in 1948 and figures prominently in review articles by Schenker and March and remains an important method of diagnosis and treatment.^{3,8,9}

However, other methods may also be used to help elucidate the diagnosis. Hysterosalpingography is a radiographic evaluation of the uterus and fallopian tubes after injection of radiopaque contrast material. It is beneficial for the gynecologist to perform this test himself or herself to benefit from real-time observation of the fluoroscopy. A reusable metal Jarcho cannula or disposable hysterosalpingography (HSG) catheter is used with appropriate sterile technique. Most commonly, water-soluble contrast material is used. Complications are few but include bleeding, infection, and crampy pain. The use of prophylactic oral antibiotics is individualized according to the patient's needs.¹⁴ Oral nonsteroidal anti-inflammatory drugs are sufficient to relieve most crampy pain. Dye reaction is very rare, as is perforation of the uterus. It is also possible to irradiate an unsuspected pregnancy, however scheduling during the proliferative phase reduces the risk. This can be impossible in the patient with amenorrhea, therefore excluding pregnancy by appropriate testing is mandatory. IUAs have a characteristic appearance of filling defects that do not change in position and need to be differentiated from polyps, fibroids, and air bubbles. In some instances, it may not be possible to pass the cannula or catheter; this further supports the diagnosis of Asherman's syndrome. It is also possible that passing the cannula or catheter may disrupt the adhesions in the cervicoisthmic junction and restore menses for some patients. Also, it should be noted that patients with sclerosis of the endometrium may have a normal-appearing HSG.

Currently, most gynecologists have ultrasound available to them in the office setting. Clearly, transvaginal and abdominal ultrasound are of limited use in the diagnosis and evaluation of IUAs. On the contrary, saline infusion sonography and three-dimensional ultrasound provide some specific information on location and extent of adhesions.¹⁵ Soares et al¹⁶ studied 65 infertile patients prospectively. They found that sonohysterography and HSG had a sensitivity of 75% for intrauterine adhesions and positive predictive values (PPVs) of 42.9% when compared with hysteroscopy as the gold standard. In this study, transvaginal sonography had a sensitivity and PPV of 0% for this diagnosis.¹⁶

The benefits of three-dimensional ultrasound or saline infusion sonogram (SIS) in preoperative staging remain to be proved. Magnetic resonance imaging

(MRI) has been described for the detection of IUAs. Letterie and Haggerty¹⁷ in 1994 and Bacelar et al¹⁸ in 1995 described the use of MRI for the diagnosis of IUAs. The former described two cases and the latter described four cases. Current literature searches reveal little regarding Asherman's syndrome but a large body of work for uterine anomalies, cancer, torsion, fibroids, adenomyosis, and other uterine conditions.

The gold standard is and should continue to be hysteroscopy for diagnosis and treatment. Indeed, the absence of adhesions on SIS or HSG should not deter one from proceeding with hysteroscopy. Hysteroscopy is widely available, and many operative instruments are available for lysis of adhesions. This technique allows the operator to assess the extent of adhesions and to proceed to lyse them under direct vision. This is in contrast with the technique of Asherman and others of blind vaginal dilatation and sometimes abdominal hysterotomy for lysis of adhesions.^{3,4,19}

The desire to predict treatment outcomes and subsequent pregnancies has resulted in numerous classification schemes being proposed. These as summarized by Al-Inany¹² range from simple such as proposed by March et al^{12,20} and Valle and Sciarra²¹ to more complex schemes proposed by Donnez and Nisolle,²² the American Fertility Society,²³ European Society Classification,²⁴ and Nasr et al.^{12,25} All of the classification systems are based on the appearance and location of the adhesions. The American Fertility Society classification and the system of Nasr et al²⁵ attempt to correlate the appearance, extent, and location of adhesions with the menstrual pattern and therefore offer some prognostic information to clinician and patient.^{12,25} The scoring and classification systems are based on small numbers and would need to be validated with much larger numbers to be clinically useful and achieve widespread use. At this time, there is no clear consensus on the best system to use.

TREATMENT

Treatment of Asherman's syndrome has evolved over the years since its initial description. Asherman treated patients either vaginally or abdominally by hysterotomy but speculated on the possible importance of hysteroscopy. Modern treatment has focused on the use of hysteroscopy with some use in combination with other imaging techniques.

In reviewing the literature, there were no randomized trials of treatment, only limited case series, case reports, and personal experience. A search of the Cochrane Library failed to reveal a review of IUAs or Asherman's syndrome treatment. Therefore, treatment is based on small case series and expert opinion. Asherman in his original works described gentle dilatation and if necessary hysterotomy and

manual lysis of adhesions.^{4,19} Since then, almost all of the case reports and series advocate the use of the hysteroscope for lysis of IUAs under direct vision.

Modern treatment of IUAs has focused on two areas: first is the actual management of the adhesions, and second is preventing adhesion re-formation. As mentioned before, hysteroscopy has become the treatment of choice with lysis of the adhesions under direct vision. Most operators choose to use a small rigid hysteroscope for this procedure with operating channel of 3- to 7-Fr diameter. This allows for the use of flexible or semirigid scissors to lyse the adhesion usually at the junction of the adhesion with the endometrium and excise the tissue. As in most hysteroscopic procedures, it is important to maintain orientation and landmarks throughout the entire procedure by keeping the camera upright and visualizing landmarks during the procedure. We use the endocervical canal, internal os, and tubal ostia once they become visible to maintain our orientation. In severe cases, it may be necessary to perform concurrent ultrasonography to facilitate passage through the endocervical canal and internal os into the cavity. We find this very helpful for the obliterated cavity and also in cases where there has been a previous false passage or perforation. Simultaneous laparoscopy may also be valuable for guidance of adhesiolysis. In this instance, turning down the light source on the laparoscope allows for visualization of the light from the hysteroscope and can help to reduce the incidence of perforation. This useful technique can be applied to septae and fibroids as well.

Several reports of the use of electrosurgery for lysis of IUAs have also been noted. This has been with both unipolar and bipolar electrodes. However, this seems to be a less popular means, and there is some concern that the injured area could re-form adhesions more readily than do areas of sharply dissected adhesions. March has maintained that the use of energy sources such as Nd:YAG laser and monopolar or bipolar instruments can cause further damage to the endometrium.²⁶ He further points out that these are the same instruments used to perform endometrial ablation.²⁶ Rarely is bleeding in the absence of perforation a problem in lysis of IUA, making the use of any source of energy largely unnecessary. Valle and Sciarra²¹ reported a very large series of cases treated by hysteroscopy. This is a retrospective analysis of 187 patients treated over 10 years and represents one of the largest series reported to date treated by hysteroscopy. All of the patients had previous endometrial trauma, except for one that had what is described as acute endometritis. They classified adhesions as mild (23.0%), moderate (51.9%), or severe (25.1%). One hundred sixty of 187 patients had concomitant laparoscopy; an intraoperative intrauterine device (IUD) was placed in 151

patients with extensive adhesions. All patients received prophylactic antibiotics, and 171 patients received conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) for one or two cycles. One hundred forty-seven of 183 patients achieved pregnancy, 79.7% term pregnancy, 18.2% spontaneous abortion, and 2.1% ectopic. Mild disease patients achieved a pregnancy rate of 81.3% and those with severe disease a 31.9% pregnancy rate. Remarkably, placenta accreta was not reported in this group of patients. Repeat procedures were not required in the mild group, 21.6% of moderate group, and 48.9% of the severe group.

Several other methods have also been presented in small series. Broome and Vancaillie²⁷ in 1994 published a series of 55 patients with adhesiolysis performed hysteroscopically and fluoroscopically. In this series of patients with severe adhesions, at least two and up to six procedures were required, and all patients resumed menstruation. There were only two minor perforations, but pregnancies were not reported. Coccia et al in 2001 reported a novel technique for treating IUAs.²⁸ They treated seven patients with "mild" and "moderate" IUA with a technique called pressure lavage under ultrasound guidance (PLUG). Two patients required repeat treatment and one was subsequently treated successfully by hysteroscopy. Two of the three infertile patients became pregnant with one normal delivery. Protopapas et al reported a small series of seven cases using a hysteroscopic technique they called myometrial scoring.²⁹ In this technique, six to eight longitudinal incisions are made in the myometrium from the fundus to the isthmus to a depth of 4 mm using a knife electrode. They reported four pregnancies in three women at 1 year, with one 36-week delivery, an ongoing pregnancy, a missed abortion, and a tubal abortion. Despite these techniques, the mainstay of therapy continues to be hysteroscopic-directed lysis of adhesions. These studies highlight the lack of randomized, large clinical trials for management of Asherman's syndrome.

The second aspect of treatment of IUAs is prevention of re-formation of adhesions. This is a significant problem that is related to the severity of the original disease. Yu and colleagues reported a rate of recurrent adhesions of 16.75% in moderate disease and 41.9% in severe disease, in contrast none in patients with mild disease.³⁰ Asherman⁴ discussed the use of a penicillin-soaked gauze inserted into the uterine cavity after every curettage to completely eradicate the problem of IUAs. Whereas this has not come to pass and Asherman's syndrome has not gone away, numerous techniques for preventing adhesions have been proposed. Some of the earliest proposals were to use nonmedicated IUDs for the purpose of preventing reagglutination of the walls of the uterus. This strategy fell by the wayside with the removal of non-copper bearing or medicated IUDs from

the U.S. market in the 1970s. In fact, while in residency this author treated several patients with Dalkon shields (Dalkon Shield, Richmond, VA) and Lippes loop (PEI, North Tonawanda, NY) IUDs after hysteroscopic lysis of adhesions. However, this is only anecdotal and hardly represents medical evidence or even the state of the art. Schenker⁹ did present evidence for the efficacy of IUD use demonstrating a 55% conception rate, 61% term labor, 75 preterm, and 7% placenta accreta. However, the type of IUD to be used or the length of time it is needed is not provided in this study.

Most gynecologists today prefer to use a balloon catheter, most often a normal Foley-type catheter or a specifically designed balloon such as the Balloon Uterine Stent (Cook Medical, Bloomington, IN). At the conclusion of the procedure, the balloon is placed in the uterine cavity and left in place. The length of time is quite variable most favoring 7 to 14 days, with some of the catheters being expelled before that time. One of the few comparative studies by Orhue et al demonstrated a statistically significant better outcome in the Foley catheter group.³¹ It should be noted that the significant difference was only in normal menses and normal HSG. There were no statistically significant differences in amenorrhea, hypomenorrhea, pregnancy, spontaneous abortion, preterm, or vaginal delivery rates. The type of IUD is not mentioned only that it should be of large surface area and inert. Those qualities effectively rule out the use of current IUDs in the United States, as the two types marketed here do not meet those criteria nor are they approved for this use.

In addition to the placement of balloon stents, the simultaneous use of antibiotics and estrogen is recommended. Prophylactic antibiotics are recommended because of the presence of the indwelling catheter and estrogen to promote the regrowth of endometrium, although no randomized controlled trials exist to confirm this. A broad-spectrum antibiotic such as doxycycline is administered for 7 to 10 days or as long as the catheter is in place. Numerous estrogen regimens have been promoted but usually are 5.0 mg CEE or its equivalent daily in divided doses for at least 30 days, followed by adding MPA or equivalent for 10 days.⁸ Several other methods for reducing re-formation of adhesions have been advocated including the use of amnion around the balloon catheter and the use of spray gel adhesion barrier after electrocautery lysis of adhesions.^{32,33} None of these methods have sufficient data to recommend them at this time.

One area that has changed over the years is the replacement of follow-up hysterosalpingogram with office hysteroscopy for reassessment of the cavity after treatment. The ready availability of office hysteroscopy and the use of small 3-mm-diameter flexible hysteroscopes have led to this change. Fumino et al in an abstract recommended early second look with a flexible

hysteroscope in the office setting.³⁴ In a similar abstract, Swedarsky et al looked at following patients postoperatively with serial flexible hysteroscopy in the office setting.³⁵ In this series of 22 patients, the mean number of follow-up procedures was three. Though still early with few patients, these two small series are intriguing as they move the follow-up out of the radiology suite and into the gynecologist's office.

OUTCOMES

The lack of a universally accepted classification system makes comparison of treatment methods difficult. In many series, restoration of menses approaches 100%.³⁶ However, many patients who present with this syndrome are interested in restoring fertility as well as menses. Fedele et al summarized these outcomes quite well in 2006 with intrauterine pregnancy ranging from 22.9 to 45.3% and live births from 28.7 to 32.1%.³⁷ Extensive review articles consistently find the same numbers with live birth rates of 32 to 76%. In most series, the more extensive the adhesions, the lower the pregnancy and live birth rate.^{8,12,38} For those patients who achieve pregnancy, there is a significant risk of complications including placenta accreta.^{39,40} Fernandez et al evaluated 64 patients with severe Asherman's syndrome and found a pregnancy rate of 43.8% and live birth rate of 32.8%. Three (14.3%) patients of 21 had either hysterectomy or hypogastric artery ligation for placenta accreta.³⁸ This is in contrast with the findings of Miller et al who found a placenta accreta rate of 1 in 2500 deliveries in an analysis from 1985 to 1994.⁴¹ However Wu et al in a review of cases from 1982 found an incidence of 1 in 533 deliveries.⁴² In both series, the main risk factors are cesarean deliveries and maternal age, however no mention of previous treatment for Asherman's syndrome is made. Nevertheless, an incidence of 3 in 21 represents a dramatic increase in this serious complication of pregnancy. Yu et al³⁰ in a recent study of 85 cases with 109 operative procedures found that women who remained amenorrheic had a significantly lower chance of conception, 18.2% versus 50%.³⁰ Similarly, the conception rate for women with a normal cavity at second-look hysteroscopy was 59.1% versus 11.8% for those who had re-formation of adhesions.

In addition to pregnancy-related complications, complications of treatment do occur. The most common potential complication is perforation of the uterus. Again because of the relatively small numbers of each case series, it is not possible to address the total number, but the incidence seems relatively low considering the difficulty of entering the cavity in many patients. Asherman's syndrome remains a significant problem even some 60 years after its initial description. Case series and expert opinion abound with few randomized clinical trials. Controversy abounds as to the best method

of diagnosis, classification, treatment, follow-up, and prevention. The issue of electrosurgery versus mechanical division for treatment also needs to be addressed, particularly in regard to re-formation of adhesions. Significant work is needed in all these areas to improve patient outcome.

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