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SYMPOSIUM: REPRODUCTIVE SURGERY
REVIEW

Management of Asherman's syndrome

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After medical school and residency, Dr. March completed a fellowship in reproductive endocrinology and infertility at the University of Southern California, where he remained for 30 years becoming professor and chief of Gynaecology. He developed protocols using injectable fertility drugs and introduced ovarian ultrasound to monitor response. He introduced a classification for intrauterine scars and a device to reduce reformation. Charles has over 200 scientific publications, has taught at universities throughout the world, and has been cited in 'Best Doctors in America' since 1992 for both reproductive surgery and endocrinology which remain the focus of his research and private practice.

Abstract Intrauterine adhesions (IUA) or Asherman's syndrome is a multifaceted condition which is being diagnosed with increasing frequency. Although it usually occurs following curettage of the pregnant or recently pregnant uterus, any uterine surgery can lead to IUA. Most women with IUA have amenorrhoea or hypomenorrhoea, but some have normal menses. Those who have amenorrhoea may also have cyclic pelvic pain secondary to 'trapped' menses and the accompanying retrograde menstruation may lead to endometriosis. In addition to menstrual disorders, most women with IUA will present with infertility or recurrent spontaneous abortion. Over the last four decades hysteroscopy has become the standard method to diagnose and treat this condition. Various techniques for adhesiolysis and for prevention of scar reformation have been advocated. The most efficacious appears to be the use of miniature scissors for adhesiolysis and the placement of a balloon stent inside the uterus immediately after surgery. Post-operative oestrogen therapy is prescribed in order to stimulate endometrial regrowth. Follow-up studies to assure resolution of the IUA are mandatory before the patient attempts to conceive as is careful monitoring of pregnancies for cervical incompetence, placenta accreta and intrauterine growth restriction.

KEYWORDS: Asherman's syndrome, endometrial sclerosis, hysteroscopy, infertility, intrauterine adhesions, intrauterine synechiae

Introduction

Intrauterine adhesions (IUA) were described initially by Fritsch (1894). Asherman (1948) brought more attention to the condition which bears his name. Some authors prefer that the term 'Asherman's syndrome' (AS) be restricted to patients with amenorrhoea, to those whose uteri are obliterated completely or to those whose scarring follows surgery on the gravid or recently gravid uterus. Others use the term 'IUA'; this term is more clear and more descriptive, but it excludes those with surface deficiencies of the endometrium without fibrous bridges between the uterine walls. These women suffer the same menstrual aberrations, infertility, recurrent pregnancy loss, intrauterine growth restriction (IUGR), errors of placental implantation and other complications of pregnancy as those with adhesions.

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Those with extensive basal layer damage, called endometrial sclerosis, have little or no functioning endometrium and thus a more dire situation. Although affixing the eponym 'Asherman's' to a condition with varying symptoms, manifestations and pathology may invite resistance, there cannot be one single definition of AS with strict inclusion and exclusion criteria: using the term 'Asherman's syndrome' signifies an endometrial disorder of great significance and one with important consequences, reproductive and other.

Most physicians believe that AS occurs rarely and do not suspect the diagnosis even in the presence of clear symptoms. **Table 1** details its prevalence among those with various conditions or after various uterine surgeries. It demonstrates convincingly that AS is anything but rare.

Epidemiology

The *sine qua non* for the development of IUA is endometrial trauma. Adhesions occur most often following curettage during or shortly after pregnancy. Friedler et al. (1993) performed hysteroscopy 4–6 weeks after dilation and sharp curettage following spontaneous first-trimester abortion. Twenty-eight (19.0%) patients had IUA: 16 of 98 (16.3%) had mild, filmy adhesions occupying more than one-quarter of the cavity after one abortion; three of 21 (14.3%) had IUA after two abortions, but after three or more nine of 28 (32.1%) had IUA. In the latter two groups, 58% of the IUA were more severe. IUA have followed evacuation of a molar pregnancy, Caesarean section, 'diagnostic' curettage, myomectomy, metroplasty or radiation. Taskin et al. (2000) detected IUA following the hysteroscopic removal of a single myoma in 31.3% of cases. This rose to 45.5% if a multiple myomectomy was performed. IUA followed hysteroscopic resection of a septum in 6.7% of the cases. These adhesions become more dense as time passes (Shokeir et al., 2008).

Although endometritis is said to be a predisposing factor, most with IUA have had no clinical evidence of infection (Polishuk et al., 1975). Infections had occurred in less than 1% of my patients. Except for the tubercle bacillus, no infectious agent causes endometrial destruction in the absence of uterine surgery.

Hamou et al. (1983) performed hysteroscopy on post-curettage patients judged to be at high risk for adhesion formation. IUA which began as thin stands progressed to thicker, more fibrous bands quickly, suggesting that prevention of IUA by reducing endometrial trauma and (perhaps) by using the prophylactic measures discussed below immediately after curettage are keys to reducing the frequency and severity of AS.

Stillman and Asarkof (1985) found Müllerian anomalies in 8.0% and AS in 4.8%, respectively of 573 infertile women. Twenty-six patients had both conditions, a highly significant correlation ($P < 0.005$). However, because spontaneous abortions occur more often in women with congenital anomalies, they will have more curettages and thus a higher rate of IUA. No data prove that the anomalous uterus is more prone to develop IUA after curettage than is a normal uterus. However, failure to completely evacuate the products of conception (POC) occurs more often among women with uterine divisions and thus prolonged retention of POC and/or repeat curettage may explain these findings (Pennes et al., 1987).

Adhesions may also develop after a diagnostic dilation and curettage (D and C). The routine use of curettage at the time of diagnostic 'infertility' laparoscopy was common decades ago and is unwarranted.

Table 1 Occurrence of intrauterine adhesions following surgery for various conditions and in those with various symptoms.

Condition/procedure	*Prevalence (%)*	*Reference*
Secondary amenorrhoea	1.7	Jones (1964)
Infertility	6.9	Nawroth et al. (2003)
Post-Caesarean section	2.8	Rochet et al. (1979)
Post-partum D and C (any time)	3.7	Bergman (1961)
Post-partum D and C (2–4 weeks)	23.4	Eriksen and Kaestel (1960)
Early spontaneous abortion D and C	6.4	Adoni et al. (1982)
Late spontaneous abortion D and C	30.9	Adoni et al. (1982)
Missed abortion	35	Schenker and Margalioth (1982)
Elective abortion D and C	13	Kralj and Lavric (1974)
Recurrent abortion	39	Toaff and Ballas (1978)
Retained products of conception	40	Westendorp et al. (1998)
Spontaneous abortion		
One	16.3	Friedler et al. (1993)
Two	14	
Three or more	32	
Hysteroscopic myomectomy		
Single	31.3	Taskin et al. (2000)
Multiple	45.5	
Hysteroscopic metroplasty	6.7	

D and C = dilation and curettage.

Polishuk and Sadovsky (1973) reported 11 patients with 'recurrent intrauterine adhesions' and suggested uterine fibrosis as the cause. However, initial treatment was by curettage and thus this 'therapy' may have caused de-novo adhesion formation or reformation of those adhesions already present. Nevertheless, because some women who conceive after treatment may be more susceptible to adhesion formation following another curettage, the study centre recommends placement of a uterine stent and oestrogen treatment to reduce the risk of scar reformation should curettage be repeated.

IUA have been diagnosed with increasing frequency over the past three decades; however, it is unclear whether the incidence is rising secondary to the performance of a greater number of, as well as more complex, uterine surgeries or if this phenomenon is secondary to increased awareness and more sensitive diagnostic procedures.

Pathology

There are three types of pathology (Foix et al., 1966). Most common is avascular fibrous strands joining uterine walls. IUA may be accompanied by deep adenomyosis. Myometrium may be present. Muscular adhesions are more dense and indicate a deficient endometrial basalis and a poorer prognosis. Some patients have only a sclerotic, atrophic endometrium and thus the worst prognosis.

Symptoms

The menstrual pattern and extent of IUA do not correlate perfectly. Toaff and Ballas (1978) reported amenorrhoea in some women with minimal IUA of the internal os and/or endocervix and suggested that a neuroreflex mechanism in that region may cause the endometrium to be unresponsive to ovarian hormones. Polishuk et al. (1977) performed pelvic angiography in 12 patients with reduced or absent menses after curettage. Seven had reduced myometrial blood flow and widespread vascular occlusion. These findings could explain endometrial atrophy, recurrent abortion, fetal death *in utero* and IUGR.

Although most of the study centre's patients had amenorrhoea, 87 (6.8%) of 1287 women had cyclic, painless menses of normal flow and duration including 2.5% of those who had extensive scarring. Taylor et al. (1981) detected IUA in 22% of normally menstruating infertile patients. Therefore, IUA cannot be excluded in women with normal menses or in those amenorrhoeic women who have withdrawal bleeding after hormone administration.

Those with hypomenorrhoea or amenorrhoea after uterine surgery should be considered to have IUA. Amenorrhoea plus premenstrual molimina or evidence of ovulation as well as the failure to have withdrawal bleeding after progestin or sequential oestrogen—progestin treatment is almost diagnostic of IUA.

Another symptom is infertility caused by obstruction of the tubal ostia or endocervix. Others have subclinical recurrent abortion caused by poor endometrial receptivity.

The consequences of AS are not limited to reproductive problems. Those with amenorrhoea or hypomenorrhoea often have scarring of the cervix or lower uterine segment. If there is functioning endometrium above these sites, the patient may have cyclic pain and, if treatment is delayed and at least one Fallopian tube is patent permitting prolonged retrograde menstruation, endometriosis may develop.

Diagnosis

If the uterine cavity cannot be sounded, scars involve at least the endocervix. However, the upper cavity may also be obliterated. Sonography can assess endometrial development, can identify areas of calcification as well as hyperechoic areas which correlate with dense adhesions and may detect a haematometra. Lo et al. (2008) reported very thin endometrium without haematometra in most women with outlet obstruction caused by IUA. Schlaff and Hurst (1995) reported that the pre-operative endometrial thickness correlated with the outcome of treatment. If uterine sounding fails, hysteroscopy should be performed rather than hysterosalpingography (HSG) or saline infusion sonogram (SIS). If a sound won't pass, neither will iodine contrast nor saline.

If a uterine sound does pass or if the patient has hypomenorrhoea, the author advises HSG. Although some recommend that hysteroscopy replace HSG for diagnosis, HSG provides information about the Fallopian tubes, is less costly and helps to plan surgery. SIS provides data about uterine structure and endometrial development but not about tubal anatomy and patency. SIS and HSG have similar high sensitivity but high false-positive rates (Soares et al., 2000). In order to consider the HSG normal, an image should be captured early in the filling phase of the study, the uterus should be parallel to the film plate and the device used to deliver the contrast should be in the cervix, not the uterine cavity. A normal, properly performed HSG eliminates the diagnosis of IUA but not of endometrial sclerosis which could be diagnosed by hysteroscopy. Three-dimensional SIS and magnetic resonance imaging (MRI) add little if IUA have been eliminated from consideration.

Table 2 Classification of intrauterine adhesions.

Class	*Extent*
Mild	Filmy adhesions in less than one-quarter of uterine cavity involved; thin or filmy adhesions Ostial areas and upper fundus minimally involved or clear
Moderate	Adhesions in one-quarter to three-quarters of uterine cavity involved; ostial areas and upper fundus only partially occluded
Severe	More than three-quarters of uterine cavity agglutinated; ostial areas and upper cavity occluded

Hysteroscopy allows direct inspection of the uterine cavity for diagnosis, classification and treatment (**Table 2**; March et al., 1978). The American Society of Reproductive Medicine Classification (1988) is a modification of this system and includes menstrual history. The clinicohysteroscopic scoring system proposed by Aboul Nasr et al. (2000) combines features of both and adds prior reproductive history, thereby enhancing its prognostic value. These systems also allow the value of different adjunctive therapeutic measures to be compared.

Do infertile patients with IUA but without other symptoms need surgery in order to conceive and have successful pregnancies? Schenker and Margalioth (1982) summarized the outcome of 292 patients with presumed IUA (few if any of these patients had the diagnosis confirmed by hysteroscopy) who attempted to conceive without treatment. Although 46% did conceive, only 30% of 165 pregnancies were delivered at term and placenta accreta occurred in 13%.

Management

Principles critical to a successful approach to AS are encompassed in the acronym 'PRACTICE': PRevention, Anticipation, Comprehensive therapy, Timely surveillance of subsequent pregnancies, Investigation, Continuing Education.

Prevention

This principle is applied in two different ways depending upon whether or not the patient is pregnant or was so recently. If faced with intrauterine fetal demise (IUFD), assess the need for surgical evacuation. If the loss occurred early, the author prescribes misoprostol shortly after the diagnosing IUFD because the likelihood of successful medical therapy decreases as the interval between demise and evacuation increases (Zhang et al., 2005). The protocol for misoprostol begins with pretreatment using ondansetron, one 8 mg oral dissolving tablet together with one hydrocodone and ibuprofen tablet 1 h prior to placing 800 μg of misoprostol vaginally. If there is little or no response, the misoprostol is repeated in 24 h. Both the ondansetron and hydrocodone/ibuprofen tablet are repeated as necessary.

If there has been a presumed passage of the products of conception an ultrasound is performed. If passage appears to be complete, 0.2 mg methylergonovine maleate is prescribed orally every 4 h for a total of six doses. If the ultrasound suggests retained POC after one dose of misoprostol, the regimen is repeated. If the treatment regimen fails, removal of the retained POC under hysteroscopic guidance is recommended. This regimen is employed up to a gestational age of 10 weeks.

Expectant or medical management after IUFD is both acceptable to patients and is as efficacious as curettage in assuring complete evacuation (Blohm et al., 1997; Smith et al., 2009). Pregnancy rates after non-surgical management of spontaneous abortion are excellent (Fontanarosa et al., 2007). Tam et al. (2002) randomized 82 patients with spontaneous incomplete abortion to observation, medical or surgical management. Outcomes were similar and hysteroscopy 6 months later detected IUA only in the post-curettage group. A high rate of spontaneous, complete expulsion of the POC following IUFD in early pregnancy has been reported in multiple studies if surgical intervention was delayed for 1 week after fetal loss had been diagnosed (Wieringa-de Waard et al., 2002). The pregnancy rate after medical management of abortions is over 80% at 1 year (Smith et al., 2009). In addition to IUA, prior uterine curettage has been reported to increase significantly the incidence of retained placenta after vaginal delivery, setting the stage for another curettage (Panpaprai and Boriboonhirundarn, 2007).

If surgery is required, it should be performed sooner rather than later because the likelihood that IUA will develop following surgery increases as the interval between IUFD and D and C is prolonged. Adhesions were found after curettage in 30.9% of women who had a missed abortion, compared with only 6.4% of those whose curettage was performed because of an incomplete abortion (Adoni et al., 1982). In women with a missed abortion, retained placental remnants may induce fibroblast activity and collagen formation before endometrial regeneration occurs. Thus, the study centre has used 3 weeks as an arbitrary cut-off period between the diagnosis of IUFD and surgical intervention. Removal of POC under hysteroscopic guidance is preferred by many but few physicians utilize this procedure. As an alternative, perform curettage under ultrasound guidance, a technique which assures that evacuation is complete and allows the surgery to be terminated as soon as complete evacuation has been documented.

If intrapartum haemorrhage occurs, the obstetrician has a 'golden' opportunity to make the diagnosis of retained POC by performing manual exploration of the uterus. Uterine exploration permits removal of all placental fragments; if bleeding occurs days or weeks later, curettage is not necessary because the physician knows that retained POC cannot be the cause. If a prior delivery had been complicated by retained POC or if the patient had undergone therapy for AS, uterine exploration at the time of delivery (rather than relying upon placental appearance to assure its completeness) offers prevention against subsequent postpartum complications related to retained POC. Golan et al. (1996) reported that after manual removal of the placenta hysteroscopy diagnosed IUA in 2% of cases. Although some have concluded that the development of the IUA was therefore a complication of the manual removal, the reason for the manual removal may have been a partial placenta accreta and the IUA which were detected subsequently had formed at the site of deficient endometrium.

Lurie et al. (1991) performed hysteroscopy after midtrimester termination of pregnancy and found a higher incidence of intrauterine adhesions (38.5% versus 7.7%) among those who underwent routine curettage following delivery of the placenta compared with those who were observed or curetted subsequently only for a presumed diagnosis of retained POC. They recommended that curettage be limited to those in whom retained POC are suspected. de Vries et al. (2000) performed ultrasound immediately after early (16–28 weeks) delivery in order to detect retained POC. They reported a sensitivity of 85% and a specificity of 88% combined with a negative predictive value of 92% and recommended that curettage not be performed in pregnancies at high risk for retained POC if ultrasound suggested an

empty uterus. The data from these two studies and the author's recommendations, if followed, would reduce the number of curettages significantly as well as the frequency of IUA and other surgical complications. If retained POC are detected, removal under hysteroscopic guidance is associated with a decreased rate of IUA formation (Dankert and Vleugels,, 2008).

A post-partum curettage is most likely to result in IUA if it is performed between 2 and 4 weeks after delivery (Eriksen and Kaestel, 1960). Within the first 48 h after delivery, the uterus is much less vulnerable to IUA formation after curettage (Eriksen and Kaestel, 1960). Women who breastfeed are at higher risk of adhesion formation because they remain oestrogen deficient for a long time, delaying endometrial proliferation (Buttram and Turati, 1977). In these instances, consider recommending that nursing be discontinued and prescribe oestrogen. If uterine exploration had not been performed but post-partum haemorrhage does occur, ultrasound may suggest that the uterus is empty and thus curettage is not necessary. If retained POC are suspected by ultrasound, medical therapy may cause their evacuation, obviating the need for curettage. In those situations in which curettage is performed, ultrasound guidance should be used (Wolman et al., 2009). Hysteroscopic guidance for removal of retained POC is less traumatic than blind D and C (Cohen et al., 2001). Following removal, prophylactic measures against the development of IUA are advised although their efficacy is unproven. Intravenous antibiotics are usually given during curettage and some recommend a brief course of oral therapy after surgery. Post-operative oestrogen therapy may promote rapid endometrial regeneration and the short-term placement of a uterine stent may prevent adhesion formation by preventing the uterine walls from remaining in apposition early in the healing phase. Farhi et al. (1993) demonstrated a significant increase in endometrial thickness and volume following oestrogen therapy after curettage for first-trimester abortion compared with patients who were not so treated but these authors did not assess either group for the subsequent development of IUA. Schenker and Margalioth (1982) used brief oestrogen therapy and placement of an intrauterine device (IUD) following curettage for a missed abortion. They reported 'most encouraging results' in the prevention of IUA although the controls were only historic. Massouras (1973) used a specially designed IUD to prevent IUA in 170 patients who had sustained various types of endometrial injury. The prophylactic use of an intrauterine stent might be warranted in those at highest risk for the development of IUA. Although the author has made these recommendations for many years and believes them to pose no harm and to be efficacious, clinical trials are necessary to prove efficacy.

With respect to uterine surgery at a time unrelated to pregnancy, four factors are associated with a greater frequency of post-operative IUA formation, as discussed below.

Gonadotrophin-releasing hormone agonist

Many surgeons prescribe a gonadotrophin-releasing hormone agonist (GnRHa) prior to abdominal myomectomy and various types of hysteroscopic surgery. If used before abdominal myomectomy, appropriate indications include the correction of anaemia, a reduction in intraoperative blood loss and/or a reduction in tumour size pre-operatively. However, as the drug-induced oestrogen deficiency progresses, the endometrium atrophies and may be damaged more easily as fibroids are separated from the overly thinned endometrium. Hypogonadotrophic hypogonadism has been shown to be associated with extensive IUA formation and so-called 'senile' adhesions have been found in post-menopausal women who had no prior instrumentation (Buttram and Turati, 1977; Panayotidis and Ranjit, 2002). The best of both worlds may be achieved by scheduling the myomectomy 7–8 weeks after the last injection of a medication such as depot leuprolide acetate. This brief delay allows ovarian function to resume, initiating endometrium regrowth and allowing less traumatic fibroid removal at a time prior to the resumption of menses or tumour regrowth.

Some (Mencaglia and Tantini, 1996) prescribe a GnRHa prior to hysteroscopic surgery in order to cause thinning of the endometrium, thereby affording a more clear view of the uterine interior, a benefit also gained by scheduling the surgery shortly after menses end. Following the induction of endometrial atrophy the basal layer is more susceptible to damage. A shorter operating time and a reduction in the amount of fluid absorbed during surgery has been reported following the administration of GnRHa prior to various types of hysteroscopic surgery (Parazzini et al., 1998), a claim disputed by others (Mavrelos et al., 2010). Irrespective of which claim is correct, the benefits claimed by Parazzini et al. (1998) were not of any clinical significance. Taskin et al. (1996) reported a high rate of IUA formation after hysteroscopic myomectomy and metroplasty when pretreatment with a GnRHa was used. Hence, for this indication, preoperative GnRHa treatment is not necessary and potentially harmful.

Incision of a uterine septum

Incision of a uterine septum is best accomplished with scissors, not electrical or laser energy. Energy spreads beyond the point of application causing collateral damage and perhaps IUA, a sequela which the author has seen on many occasions among patients treated in this manner. Moreover, Candiani et al. (1991) demonstrated that scissor incision of a septum was as effective as a laser in treating septa and required less operating time. In contrast, Cararach et al. (1994) reported that operating times were significantly longer (but not of clinical significance) when scissors rather than a resectoscope were used to treat the anomaly. Moreover, DeCherney et al. (1986) reported inability to complete hysteroscopic resection of a septum in 30 of 103 patients so treated and Cararach et al. (1994) reported a significantly lower pregnancy rate (67.9% versus 88.2%, $P < 0.05$) when a resectoscope was used to treat a septum compared with scissor incision. Post-operative IUA have not been detected in the study centre's series of over 500 hysteroscopic metroplasties performed with scissors. Although some have suggested that haemostasis is better achieved when an energy source rather than scissors is used for septoplasty, significant bleeding at the site of septal incision has not been encountered in this series; the few instances of mild bleeding have occurred only when the dissection was continued

into the myometrium. In all instances, the bleeding resolved quickly.

Hysteroscopic myomectomy

Hysteroscopic myomectomy is usually performed with a resectoscope. By using the lowest effective power setting and delivering the energy in the pure-cut mode, this risk is reduced greatly.

New instrumentation and technologies

The introduction of new instrumentation and technologies into the field of reproductive surgery benefits all. Initial studies to prove safety and efficacy are performed by expert surgeons. However, after these instruments are marketed, they are often used by those with little or no training, increasing the risk of excessive uterine damage. With the advent of oocyte donation and gestational carriers, some practitioners have concluded that the need to protect reproductive organs from further damage is less important. Thus, the emphasis upon meticulous reproductive surgery has diminished. Many reproductive endocrinology and infertility specialists limit their practices to assisted reproductive technology and perform little or no reconstructive pelvic surgery, leaving these procedures to general gynaecologists who often had little experience with these procedures during their gynaecological training and whose post-residency experience did not add significantly to their expertise. The Society of Reproductive Surgeons has recognized this fact and the concern raised above about the introduction of new instrumentation into the specialty of reproductive surgery and has co-sponsored, along with the American Association of Gynecologic Laparoscopists, an Advanced Endoscopy Fellowship (Azziz, 2002). All too often both the generalist and the infertility specialist subscribe to the thinking that 'there is always IVF' and/or surrogacy. Although the advent of new assisted reproductive technology modalities is most welcome, they are not for all women, whether the objection is cost, personal or the desire to conceive, carry and deliver an infant of their own genetic makeup.

Anticipation

Clinicians should anticipate who may develop AS. The highest risk is for those who undergo curettage 2—4 weeks after delivery, for those who have been treated for recurrent losses by repeated curettage, for those curetted multiple times during/after the same pregnancy and for those undergoing surgery while oestrogen deficient. Therefore, if curettage is deemed necessary, it should be done under ultrasound guidance and consider using the prophylactic measures of stent placement and oestrogen therapy.

Comprehensive therapy

For decades, the study centre has used a multifaceted approach to the treatment and follow-up of AS (**Table 3**). Repair of the uterus under direct visualization was proven (Levine and Neuwirth, 1973) to be superior to blind curettage in the early 1970s. Lysis of adhesions under direct vision permits the surgeon to cut only scar tissue, reducing trauma to normal endometrium; thus, it is safer and more complete than blind curettage. A continuous-flow hysteroscope is used and the cavity is distended with a low-viscosity fluid. Miniature scissors incise rather than excise each adhesion, because excision risks further injury to the endometrial basalis. Some follow hysteroscopic treatment with curettage to 'remove' the cut scars, an approach which is neither necessary nor wise. Careful monitoring of fluid balance via a fluid management system, which provides real-time data regarding the amount of fluid used as well as the deficit, is utilized and is critical to patient safety. If a large amount of fluid is absorbed during surgery and the surgeon believes that the risk of fluid overload is high, a diuretic may be administered intravenously during surgery or the procedure can be discontinued and completed at a later date. Complete adhesiolysis can be achieved even in women with extensive disease.

Table 3 Protocol for managing intrauterine adhesions.

Goals	*Means*
Repair cavity	Scissor lysis under direct visualization
Prevent rescarring	Intrauterine stent
Promote healing	High-dose oestradiol
Follow-up	
Architecture	Hysteroscopy or hysterosalpingogram
Function	Mid-cycle ultrasound of the endometrium

In some instances, even after extensive hysteroscopic adhesiolysis, intrauterine landmarks remain obscure; in others, entry into the uterus is not possible and thus the risk of uterine perforation is high should the hysteroscopic approach continue unassisted. Two alternatives provide safety and reduce the risk of perforation. In these instances and for those who have suffered one or more uterine perforations previously, the study centre performs simultaneous laparoscopy. Following a survey of the pelvis and correction of any endometriosis and/or pelvic adhesions, the intensity of the light source for the laparoscope is reduced markedly. The hysteroscopic adhesiolysis is begun and the laparoscopist monitors the intensity of the hysteroscopic light which is transmitted through the uterine wall. If the uterus glows uniformly, it is presumed that the hysteroscopist is in the proper plane of dissection and that the risk of perforation is low; if instead, a bright, well-focused beam of light shines through the uterine muscle, it is likely that perforation is imminent and the plane of dissection is altered. With this combined approach, only one perforation has occurred.

The complication rate has been low: 64 complications in 1493 procedures. In 46 women there was bleeding at the site of tenaculum placement. Two others had intrauterine bleeding which was controlled with placement of a balloon for 24 h. Seven patients were hospitalized for fluid

Table 4 Cumulative negative effect of multiple uses of energy during hysteroscopic adhesiolysis on the success of subsequent therapy.

Therapy	*Normal HSG/HSC*	*Pregnant*[a]
Overall	945/1221 (77.4)	764/1240 (61.6)
One prior operation (362)	163/362 (45.0)	99/362 (27.3)
With energy (301)	131/301 (43.5)	83/301 (27.6)
Without energy (61)	32/61 (52.5)	16/61 (26.2)
Two prior operations (124)	42/124 (33.9)	21/124 (16.9)
With energy (110)	34/110 (30.9)	17/110 (15.5)[b]
Without energy (14)	8/14 (57.1)	4/14 (28.6)

Values are *n*/total (%).
HSC = hysteroscopy; HSG = hysterosalpingography.
[a]Includes 19 patients who had neither an HSG nor a hysteroscopy as a method of follow-up.
[b]$P < 0.05$ versus surgery without the use of energy.

overload. Six of these had received at least 600 ml of high-molecular-weight dextran (a medium no longer used for hysteroscopic surgery) to distend the uterus and also had disseminated intravascular coagulation. There were eight midline fundal perforations, none of which required treatment. One patient became febrile 2 days after surgery and received antibiotics. Others have reported complication rates to be between 1.1% and 9%, with perforation and haemorrhage being the most common complications (Yu et al., 2008).

This approach has resulted in an overall success in restoring uterine architecture to normal (as judged by HSG or in-office hysteroscopy) of 77.4% and a pregnancy rate of 61.6% (**Table 4**). As would be expected, those who had one prior attempt at cure elsewhere had a significantly poorer anatomic outcome and a lower pregnancy rate. These results were even worse if two prior attempts elsewhere had been unsuccessful.

Rock et al. (1993) described a modified laparoscopic approach for patients with extensive, dense adhesions of the cervix and lower uterine segment which precluded safe entry into a scar-free upper fundus. During laparoscopy they injected a solution of methylene blue into fundal cavity and the hysteroscopist reached that site by directing the plane of dissection towards the blue-stained upper cavity.

Others use ultrasound to image the endometrium and provide a 'target' for the hysteroscopic dissection (Dabirashrafi et al., 1992). This approach is of value for those with significant lower segment scarring but whose upper cavities are damaged only moderately or less. If there is significant lateral or marginal scarring, the ultrasound images may not prevent dissection into the myometrium and even uterine perforation.

Others treat adhesions via electrosurgery or a laser. Protopapas et al. (1998) described myometrial scoring, using an electrosurgical knife to cut radial incisions into the myometrium in patients with tubular uterine cavities, allowing them to open like an accordion and hopefully allow endometrium to migrate over the incised surfaces. Some claim that scars are too dense to cut with scissors and that the use of energy sources results in less bleeding (Chapman and Chapman, 1996; Newton et al., 1989). However, the author has used only scissors successfully in more than 1500 procedures; moreover, it is myometrium, not scars, that bleeds. Although advocates claim that the collateral thermal damage is minimal, thermal injury spreads well beyond the site of application (Panayotidis et al., 2009; Duffy et al., 1992). Although such spread is only 2 mm with a potassium-titanyl-phosphate (KTP) laser, the depth of injury approaches 1 cm with an neodymium-doped yttrium aluminium garnet (Nd:YAG) laser. If a bipolar electrode is used, the collateral damage is less than that caused by monopolar electrodes, especially if the monopolar energy had been applied in the coagulation mode. Finally, it is counterintuitive to use the same instruments which cause the necrosis desired to cause endometrial ablation in an area of damaged endometrium. Yu et al. (2008) reported that four of 85 (4.7%) patients had progressive disease after hysteroscopic adhesiolysis using a needle or loop electrode with combined cutting and coagulating current. Patients referred for treatment of IUA who had undergone surgery elsewhere during which energy had been used twice or more had a poorer prognosis compared with those whose prior procedures had been performed without energy (**Table 4**), suggesting that the repetitive energy use had resulted in progressive uterine damage.

Ikeda et al. (1981) used blunt disruption of focal adhesions with an insemination catheter filled with an iodine contrast medium. By having a continuous, ongoing HSG, complete adhesiolysis can be assured. An extension of this approach is placement of a balloon catheter and instillation of a radio-opaque dye in order to outline the adhesions which are then divided by microscissors passed through another channel of the catheter (Karande et al., 1997). The dose of radiation should be minimal in those with mild IUA, but might be unacceptably high in those with extensive disease.

Broome and Vancaillie (1999) placed a 16-gauge, 80-mm Touhy needle alongside a diagnostic hysteroscope and injected a radio-opaque dye through the needle which was advanced into pockets of endometrium identified by a prior ultrasound. Once these pockets have been identified

fluoroscopically, the adhesions are lysed using either the same needle or with hysteroscopic scissors. The total fluoroscopy time was approximately 30 s.

Pressure lavage under guidance involves adhesion disruption by continuous intrauterine injection of saline under ultrasound guidance (Coccia et al., 2001). This technique may disrupt mild, filmy adhesions but the data are too few to recommend its general application.

Hysterotomy is performed rarely for patients whose extensive adhesions of the endocervical canal and lower uterine segment prevent access to the upper fundus even under laparoscopic or ultrasound guidance (Reddy and Rock, 1997). Pre-operative ultrasound or MRI is essential to verify that a pocket of normal endometrium is present. If none can be detected, complete obliteration can be diagnosed and surgery is unwarranted. The pre-operative imaging study allows the surgeon to plan the site of entry into the uterus. The lower uterine segment and endocervical canal adhesions are disrupted from above with a dilator and a stent is placed into the uterus. The stem of the stent is passed into the vagina in order to splint the endocervical canal and to prevent re-adherence. Antibiotics are prescribed while the stent is in place.

Serum may ooze from the areas of the freshly dissected scars, promoting scar reformation. Thus, a non-reactive uterine stent is placed in the uterine cavity in order to keep the raw, freshly dissected surfaces separated during the initial post-operative healing phase. Polishuk et al. (1969) reported that by following adhesiolysis with IUD placement, the rate of adhesion reformation was only 10%. In contrast, in a prior series of patients treated without an IUD, the recurrence rate was above 50%. Previously, the study centre has used an inert Lippes Loop IUD. This device is no longer available in the USA. 'T'-shaped devices have a surface area too small to maintain separation of the uterine walls and thus prevent adhesion reformation. Those which contain copper induce an excessive inflammatory reaction. Devices which release a progestin into the endometrium prevent the desired proliferation produced by the post-operative oestrogen therapy. Therefore, their use is not advised.

A Cook balloon uterine stent (**Figure 1**) which, because of its triangular shape, conforms to the configuration of a normal uterus and maintains separation at the margins of the uterine cavity, which is where reformation is most common, is placed immediately after completing adhesiolysis. If the scarring is limited to the endocervical canal and region of the internal cervical os, a 12 French Foley catheter is used. After inflating the Foley balloon, heavy silk ligatures are placed around the catheter as it emanates from the cervix and the distal end is removed. The duration that a stent remains in place is based upon the extent and density of the scarring. A broad-spectrum antibiotic is prescribed during the time that the stent is in place.

The use of oestrogen to promote endometrial overgrowth and re-epithelialization of the scarred surfaces is standard. Oral micronized oestradiol, 2 mg twice daily, is prescribed for 30–60 days and medroxyprogesterone acetate, 10 mg daily, is added during the last 5 days of oestrogen therapy.

The importance of a post-operative study to verify normalcy of the cavity prior to permitting conception cannot be overemphasized. Severe obstetric complications have been reported in patients who conceived prior to having post-operative studies performed to document complete resolution of the adhesions (Deaton et al., 1989; Jewelewicz et al., 1976). In the study centre's experience, not one patient who had a normal post-treatment hysterogram (or hysteroscopy) and mid-cycle ultrasound of the endometrium prior to conceiving had an adherent placenta, in contrast to the 5–31% frequency of placenta accreta reported in prior studies (Schenker and Margalioth, 1982). Following withdrawal bleeding, the study centre assesses cavity by HSG or in-office hysteroscopy. The latter offers the advantage of permitting further adhesiolysis if there has been a partial

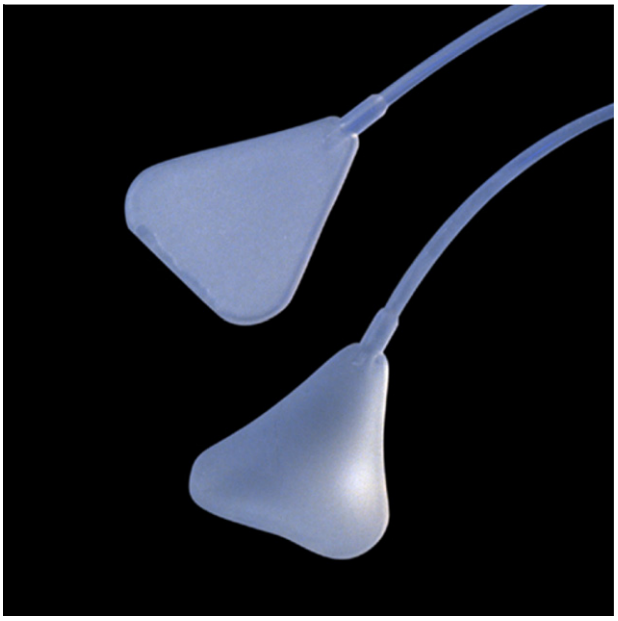

Figure 1 Cook balloon uterine stent deflated and filled with 1.0 ml of saline.

Table 5 Fertility and pregnancy outcome in women treated for Asherman's syndrome.

Outcome	*Patients (n = 1240)*
Patients clinically pregnant	764 (61.6)
Clinical pregnancies	807
Spontaneous abortion	126 (15.6)
Elective or therapeutic abortion	6
Ectopic	1
Live birth	674 (83.5)
Term	627 (93.0)
Premature	47 (7.0)
Cervical incompetence	13 (1.9)
Placenta accreta	13 (1.9)
Hysterectomy	4
Intrauterine growth restriction	3

Values are *n* or *n* (%).

recurrence. If an HSG was used as a follow-up method, the films are reviewed rather than accepting the 'official report'. If the HSG was normal, mid-cycle ultrasound of the endometrium was performed to assess endometrial development. If there had been significant improvement in uterine architecture and endometrial development, but persistent scarring remained, patients were offered another surgery.

The results with this protocol are summarized in **Table 5**. The spontaneous abortion rate (15.6%) is not higher than that among women who conceive without a history of IUA. The same is true for the frequency of prematurity which was 7.0% in this series. This rate is considerably lower than the 25–50% reported in some series (Roge et al., 1997; Zikopoulous et al., 2004). However, 13 pregnancies (1.9%) were complicated by cervical incompetence versus an expected rate of 0.1–0.5% (Lindegaard, 1994). Presumably, the repeated cervical dilations from both the curettage(s) which preceded the development of IUA as well as the dilation(s) performed during therapy contributed to cervical insufficiency. Therefore, careful monitoring of cervical length (Owen et al., 2004) as well as funnelling of the membranes (Novy et al., 2001) should be part of the obstetric management for patients who have had multiple cervical dilations. Placenta accreta occurred in 1.9% of pregnancies and four of these 13 patients underwent hysterectomy. Although the incidence of placenta accreta was one in 30,000 deliveries 50 years ago, this rate is increasing, presumably because of the increasing incidence of Caesarean section and myomectomy and of increasing maternal age (Al-Serehi et al., 2008; Miller et al., 1997). Although the frequency reported herein is well above the baseline incidence, it is lower than the 5–31% incidence reported in other series of post-Asherman's pregnancies (Jewelewicz et al., 1976; Schenker and Margalioth, 1982). **Table 6** summarizes data from seven published series which reported 50 or more pregnancies after treatment of IUA as well as the results reported from this centre. Although many of these reports do not include complete information regarding prematurity, cervical incompetence, placental problems and other specifics, they do indicate that meticulous treatment protocols are likely to be successful.

The overall pregnancy rate following treatment of IUA is approximately 30–75% (Yu et al., 2008). Valle and Sciarra (1988) reported that the pregnancy and term pregnancy rates were significantly higher in those with minimal disease (93.0% and 87.5%, respectively) compared with those with severe IUA (57.4% and 55.6%, respectively). Some authors have reported that although more than 62% of those under age 35 conceived, only 23% or less of those over 35 did so (Capella-Allouc et al., 1999; Fernandez et al., 2006), a finding disputed by others (Zikopoulous et al., 2004). Unfortunately neither the ages of those who did not conceive nor data about the presence or treatment of other infertility factors were reported. In neither report was a correlation made between the results of surgery and pregnancy occurrence or outcome. Roge et al. (1997) identified one or more additional infertility factors in 60% of those who did not conceive initially and stressed the need for a complete evaluation. In the study centre's experience, a normal post-operative study has forecasted a high pregnancy rate. The gestational outcome among those with a normal uterus has been identical irrespective of the pretreatment extent.

Five series have demonstrated a marked improvement in the gestational outcome after lysis of adhesions in patients with previous poor outcomes, improving a pretreatment successful pregnancy outcome of 25.7% (260 of 1013 pregnancies) to 79.3% (237/299 pregnancies) (Caspi and Perpinial, 1975; Lancet and Kessler, 1988; March and Israel, 1981; Oelsner et al., 1974; Valle and Sciarra, 1988). Katz et al. (1996) reported similar results.

Four factors independently reduce significantly the success of treating IUA: (i) the use of a GnRHa prior to hysteroscopic myomectomy; (ii) breastfeeding for 3 or more months among those who underwent post-partum curettage; (iii) post-partum curettage 2–4 weeks after delivery;

Table 6 Gestational outcome following treatment for Asherman's syndrome in series reporting 50 or more pregnancies.

Reference	*Patients pregnant*	*Clinical pregnancies*	*Live births*	*Premature*	*SB*	*CI*	*AB*	*Ect P*	*IUGR*	*Placenta acc/prev*
Aboul Nasr et al. (2000)	50	62	35[a]	9 (4 NND)	—	—	13	2	—	2
Feng et al. (1999)	156	156	145 (93)	0	0	—	11	0	—	4 (3)
Katz et al. (1996)	66	66	46 (70)	1 (NND)	—	—	15	—	—	—
Lancet and Kessler (1988)	86	135	77 (64)	Same	—	—	—	—	—	Same
Parent et al. (1988)	107	107	91 (85)	—	—	—	—	—	—	—
Sugimoto (1978)	79	>90[b]	45 (57)	2	3	—	29	—	—	8
Valle and Sciarra (1988)	143	—	114 (80)	—	—	—	26	3	1	2
Study centre	764	807	674 (84)	47 (7)	0	13	132	1	3	13 (2)

Values are *n* or *n* (%) unless otherwise stated.
AB = spontaneous or therapeutic abortion; acc/prev = accreta or previa; CI = cervical incompetence; Ect P = ectopic pregnancy; IUGR = intrauterine growth restriction; NND = neonatal death; Same = same as general population; SB = stillborn; — = not stated.
[a]Three pregnancies were ongoing.
[b]Eleven patients had two or more pregnancies.

Table 7 Adverse effects of various factors upon the prognosis of hysteroscopic lysis of intrauterine adhesions.

Factor	*Normal HSG/HSC*	*Pregnant*
Use of GnRHa before myomectomy	22/121 (18.2)	16/121 (13.2)
Yes (n = 84)	4/84 (4.8)	4/84 (4.8)
No (n = 37)	18/37 (48.6)[a]	12/37 (32.4)[a]
Post-partum breastfeeding (≥3 months)		
Yes (n = 198)	79/198 (39.9)	36/198 (18.2)
No (n = 98)	75/98 (76.5)[b]	87/98 (88.8)[b]
Curettage 2–4 weeks post-partum		
Yes (n = 268)	140/268 (52.2)	112/268 (41.8)
No (n = 16)	14/16 (87.5)[c]	11/16 (68.8)[c]
Myometrium in curetting		
Yes (n = 52)	11/52 (21.2)	5/52 (9.6)
No (n = 209)	133/209 (63.6)[d]	118/209 (56.5)[d]

Values are n/total (%).
HSC = hysteroscopy; HSG = hysterosalpingography.
[a] $P < 0.005$ versus myomectomy without pretreatment with a gonadotrophin-releasing hormone agonist.
[b] $P < 0.005$ versus not breastfeeding.
[c] $P < 0.05$ versus curettage at a time other than 2–4 weeks post-partum.
[d] $P < 0.01$ versus finding myometrium in curetting.

and (iv) the presence of myometrium in the curettings of those who underwent post-partum D and C (**Table 7**). The latter may be a finding which is under-reported (Beuker et al., 2005).

Pre-operative GnRHa therapy and post-partum breastfeeding may be considered together because both induce and maintain an atrophic endometrium, facilitating significant damage to the endometrial basalis. If used prior to abdominal myomectomy, GnRHa therapy causes the planes of dissection to be difficult to separate, thus facilitating endometrial damage during dissection of myomas which are near to, or impinge upon, the endometrial cavity (Deligdisdi et al., 1997). If used prior to hysteroscopic myomectomy, the electrical energy is applied closer to the endometrial basalis, increasing the risk of permanent damage. This fact is used to advantage by physicians who pretreat patients with a GnRHa prior to performing an endometrial ablation.

Post-partum breastfeeding maintains oestrogen deficiency and facilitates damage to the endometrial basalis at a time when resumption of ovarian function may have been protective. Curettage 2–4 weeks after delivery was demonstrated by Eriksen and Kaestel (1960) to be associated with a high rate of amenorrhoea and scar formation, perhaps because of the marked inflammatory process at this time and because the walls of the involuting uterus are maintained in close apposition at this time. Eriksen and Kaestel (1960) did not comment upon breastfeeding or the presence of myometrium in the curettings as an additive cofactor in inducing post-curettage amenorrhoea. The presence of myometrium in curettings is evidence of permanent damage to the uterine interior with an area of deficient endometrium. This same deficiency occurs after hysteroscopic myomectomy and may facilitate the development of placenta accreta in subsequent pregnancies.

Timely surveillance of subsequent pregnancies

Monitoring of pregnancies which occur after the treatment of AS takes two paths: one is related specifically to the AS and the other is not. Many with AS have had recurrent losses. Although the diagnosis of IUA may have been made only after multiple miscarriages (and curettages), scarring may have formed after the initial curettage, after the last D and C or at some point in between. Although the association between AS and recurrent miscarriage is clear, the inability to determine the onset of the AS with certainty mandates that all those with AS who have suffered multiple pregnancy losses undergo a complete investigation rather than assuming that the intrauterine scarring has been the cause (March, 1996).

A combination of delayed childbearing, of multiple losses and of a delay in diagnosis often results in post-AS pregnancies occurring in women who are older and may have other factors needing treatment during early pregnancy. Therefore, careful monitoring of these pregnancies IS important.

Many with AS have had repeated cervical dilations because of curettage(s) and hysteroscopies. These repeated dilations may have caused permanent damage to the cervix, leading to incompetence with pregnancy loss late in the second trimester or very premature delivery. Therefore, those who have had multiple procedures should be assessed for shortening of the cervix and for 'beaking' or funnelling of the membranes. The occurrence of either of these changes signals the need for a cerclage.

For those who have had placenta accreta previously and for those who are at high risk of this complication (the presence of myometrium in curettings or after the hysteroscopic removal of a large type I or type II (Wamsteker et al., 1993) fibroid which would by necessity have left a significant portion of the uterine wall denuded of endometrium),

should undergo an MRI or high-resolution ultrasound in late pregnancy to detect this condition (Dwyer et al., 2008). For those who are at high risk of placenta accreta, the study centre recommends that delivery be planned to occur early on a weekday, times when the hospital, interventional radiology, laboratory and blood bank are fully staffed. Warshak et al. (2010) reviewed the obstetric records of 99 women with proven placenta accreta, 62 of whom had the diagnosis made prior to delivery and 37 who did not. In the former group the intrapartum blood loss was less as was the amount of blood products received. The authors recommended elective delivery at 34—35 weeks in order to reduce the morbidity associated with emergency hysterectomy. They also advised planned Caesarean hysterectomy without placental removal be considered as the method of therapy.

Although IUGR has occurred only thrice in the study centre's large series of post-AS pregnancies, a lower incidence than that reported in the general obstetric population (Neerhof, 1995), this condition has been reported to be more frequent among those who conceive after treatment of AS, perhaps because of endometrial deficiency which hinders placental development (Yu et al., 2008).

Following vaginal delivery after treatment of AS, the uterus must be explored. The most meticulous inspection of the placenta may fail to detect its 'incompleteness' and a fragment or accessory lobe may remain, to cause haemorrhage subsequently and still another curettage.

Investigation

Asch et al. (1991) inserted oestrogen fibre-wrapped IUD into the uteri of castrated rhesus monkeys. The devices induced marked endometrial proliferation and the authors suggested that such a device might provide the same efficacy as oral oestrogen treatment but without the systemic side effects. Tourgeman et al. (1999) demonstrated that the vaginal administration of micronized oestradiol was more effective in raising endometrial concentrations of oestradiol than was the oral route of administration.

Despite the restoration of uterine architecture by surgery, the problems of adhesion reformation and endometrial deficiency remain. One approach to adhesion reformation is the use of stents which maintain the freshly dissected surfaces apart during the immediate post-operative period. Others perform frequent office hysteroscopies soon after the initial procedure when any reforming scars are thin and filmy and easily lysed (Robinson et al., 2008). This approach seems ideal but involves more cost and perhaps risks. Randomized trials of these approaches are needed.

The uterine cavity has also been filled with the abdominal anti-adhesion barrier SprayGel (mainly polyethylene glycol) after adhesiolysis (Abbott et al., 2004). The material is absorbed slowly over the next 7—21 days. Data regarding efficacy are sparse and no trials of SprayGel for this purpose have been initiated in the USA. Mohamed and Abd-El-Maeboud (2006) placed amniotic membrane around a balloon catheter. Success was limited and the data are very sparse. Seprafilm (hyaluronic acid and carboxymethylcellulose), used commonly after abdominal surgery, is not practical for intrauterine use (Tsapanos et al., 2002). Hyaluronic acid gel is also under investigation (Acunzo et al., 2003).

High-dose oestrogen therapy has been the prime method of stimulating endometrial growth after surgery. Not all patients respond and in some, the benefit is only transient. Women who fail oestrogen therapy may be those with damage to the endometrial basalis, those with myometrial fibrosis and those with vascular insufficiency, e.g. after uterine artery embolization. Some studies using sildenafil (Viagra), 100 mg vaginally or 6 mg of L-arginine (which may strengthen blood vessels) daily have shown increased endometrial thickness and an improvement in radial artery-resistance indices (Takasaki et al., 2008). There are encouraging, but scanty data demonstrating thickened endometrium after 6 months use of pentoxifylline (800 mg/day) and vitamin E (1000 IU/day). Some of those who had benefited had undergone radiation therapy, raising the possibility that these medications may bypass or reverse fibrosis. Vitamin E may also improve glandular epithelial growth, development of blood vessels and vascular endothelial growth factor protein expression in the endometrium (Acharya et al., 2009).

Continuing education

The Asherman's Online Community (www.ashermans.org) and the website www.DandCnow.info are valuable resources for patients. These sites and continuing medical education courses and the literature should guide most patients and their physicians through the daunting process of prevention, anticipation, diagnosis, treatment and follow-up.

Conclusion

A comprehensive approach to IUA including early diagnosis, meticulous surgery, modalities to reduce scar reformation, documentation of cure prior to permitting patients to try to conceive and ongoing surveillance of pregnancies up to and including delivery has been demonstrated to optimize outcome. Among those who have suffered repeated spontaneous pregnancy loss, a comprehensive evaluation of the couple in order to detect other causes for repeated miscarriage is mandatory.

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