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# Diagnosis and Treatment of Intrauterine Adhesion

*Umme Salma, Dabao Xu and M.D. Sayed Ali Sheikh*

Department of Gynecology and Obstetrics, Xiangya 3rd Hospital, Central South University, China

**Abstract:** Intrauterine adhesions develop as a result of intrauterine trauma. The degree of adhesion formation and the impact of the adhesions on the contour of uterine cavity vary greatly. It has been reported that intra abdominal adhesions occur in 60-90% of women who have undergone major gynecological procedures. Hysteroscopy is the gold standard for the diagnosis of severe intrauterine adhesions. Effective methods for preventing adhesions, a variety of surgical techniques and agents have been advocated for the prevention of intrauterine adhesion formation. The present review indicates that there is still no single modality proven to be unequivocally effective in preventing post-operative adhesion formation either for laparoscopic or for hysteroscopic use. Hopefully, the increasing understanding of the future emphasis will probably be on a multimodality therapy, including the use of pharmacologic adjutants in conjunction with a barrier material tailored to the specific operative procedure and a precise surgical technique.

**Key words:** Intrauterine adhesion (IUA) · Hysteroscopic · Pharmacologic adjutants

## INTRODUCTION

Intrauterine adhesions are a recognized complication of operative hysteroscopy. Amenorrhea associated with intrauterine adhesions was first described in 1894 by H. Fritsch in a patient after postpartum curettage [1]. Subsequently, in 1948 and 1950 J.G. Asher man published two reports [2]. On the frequency and the etiology of intrauterine adhesions and the eponym Asher man's syndrome has been used ever since. Intrauterine adhesions develop as a result of intrauterine trauma. Adhesions are defined as abnormal fibrous connections joining tissue surfaces in abnormal locations [3]. Diamond and Hellebrekers divided adhesions into two types, primary or de novo adhesions (those that are freshly formed, on locations where no adhesions were found before) and secondary or reformed adhesions (those adhesions that undergo adhesiolysis and recur at the same location [4]. Another type is modified classification based 0n European society of gynaecological endoscopy (ESGE) Table 1 in gynaecology, adhesions can be differentiated on the basis of location, into intraabdominal or intrauterine. The most frequent cause of their formation is post-partum or post-abortion overzealous dilatation and curettage. Transperitoneal operation can lead to the formation of intraabdominal adhesions ranging from minimal scarring of serosal surface to firm agglutination of nearly all structures. The formation of adhesions following open gynecological surgery has a considerable epidemiological and clinical impact. It has been reported that intraabdominal adhesions occur in 60-90% of women

Table 1: Modified classification based on European Society of Gynaecological Endoscopy (ESGE)

| Modified grade | ESGE grade | Extent of intrauterine ashesuions |
|---|---|---|
| Mild | l | Thin or filmy adhesions |
| | ll | Singular dense adhesion |
| | lla | Occluding adhesions only in the internal cervical os |
| Moderate | ll | Multiple dense adhesions |
| | lV | Extensive dense adhesions with (partial) occlusion of the uterine cavity |
| | Va | Extensive endometrial scarring and fibrosis in combination with grade l or ll adhesions |
| | Vb | Extensive endometrial scarring and fibrosis |

**Corresponding Author:** Dabao Xu, 138, Tongzipo Road, Changsha, Hunan, 410013, P.R. China.
Tel: 008673188618019, Fax: 008673188618019, E-mail:xudabao@hotmail.com.

who have undergone major gynecological procedures [5]. (The study) conducted in Scotland reported that women undergoing an initial open surgery for gynecological conditions had a 5% likelihood of being rehospitalized because of adhesions over the next 10 years and overall and adhesions may have contributed to rehospitalization in an additional 20% of patients. In recent years, many attempts have been made to develop effective strategies to reduce the risk of post-surgical adhesions [6].

**Prevalence and Symptomatology:** Intrauterine adhesions, also known as synechiae, are found in 1.5% in women who undergo hysterosalpingography [7]. Asher man's syndrome, also called "uterine synechiae" or intrauterine adhesions, presents a condition characterized by the presence of scars within the uterine cavity. Patients with intrauterine adhesions usually present with infertility, menstrual cycle disorders, repeated pregnancy losses, or abnormal adherence of the placenta [8]. Intrauterine adhesions can be asymptomatic and of no clinical significance. Symptoms associated with clinically significant intrauterine adhesions include: Infertility Menstrual irregularities (hypo menorrhea, amenorrhea) cyclic pelvic pain recurrent pregnancy loss. Disorders of placenta ion, including placenta accrete and previa, are relatively rare [9]. The condition was found in 1.5% of women undergoing HSG [16] between 5 and 39% of women with recurrent miscarriage [10] and up to 40% of patients who have undergone D&C for retained products of conception.

**Etiology:** Approximately 90 percent of cases of severe intrauterine adhesive disease are related to curettage for pregnancy complications, such as missed or incomplete abortion, postpartum hemorrhage, or retained placental remnants. Pregnancy is the most common predisposing factor, usually associated with trauma to the endometrial, as seen in patients undergoing curettage in the puerperium, after missed abortion, evacuation of a hydatidiform mole, or cesarean section. Postpartum curettage is most likely to cause intrauterine adhesions when performed between the second and fourth weeks postpartum. Repeated curettage for pregnancy loss increases the risk of developing adhesions from 8 percent after the first curettage to over 30 percent with the third curettage.

It is estimated that up to 5% of D&Cs result in intrauterine adhesions. More conservative estimates put this rate at 1%. Intrauterine adhesions results from 25% of D&Cs performed 1-4 weeks post-partum [11]. 30.9% of D&Cs performed for missed miscarriages and 6.4% of D&Cs performed for incomplete miscarriages. In the case of missed miscarriages, the time period between fetal demise and curettage increases the likelihood of adhesion formation to over 30.9% [12]. The risk of intrauterine adhesions also increases with the number of procedures: one study estimated the risk to be 16% after one D&C and 32% after 3 or more D&Cs. AS can also result from other pelvic surgeries including Cesarean sections [13]. Chronic endometritis from genital tuberculosis is a significant cause of severe IUA in the developing world, often resulting in total obliteration of the uterine cavity which is difficult to treat [14]. One study found a significant correlation between Müllerian anomalies and IUA. This apparent correlation is because women with congenital uterine anomalies are predisposed to miscarriages [15] and therefore would also have higher rates of D&Cs performed than the general population, which could account for the higher rate of IUA observed. It is also feasible that women with septate uteri and other Müllerian defects are at a higher risk of sustaining endometrial damage after blind D&C due to their atypical anatomy. An artificial form of Asher man's syndrome can be surgically induced by endometrial ablation in women with excessive uterine bleeding, in lieu of hysterectomy. In the developing world, genital tuberculosis is a cause of intrauterine adhesions, which are often severe with complete obliteration of the uterine cavity [16].

**Diagnosis:** Hysteroscopy is the gold standard for diagnosis [17]. Imaging by sonohysterography or hysterosalpingography will reveal the extent of the scar formation. Ultrasound is not a reliable method of diagnosing intrauterine adhesion. Hysteroscopy Fig. 1 is better for view.

**Strategies for Adhesion Prevention:** Effective methods for preventing adhesions, a variety of surgical techniques and agents have been advocated for the prevention of intrauterine adhesion formation. The main approaches include adjusting surgical techniques, minimizing tissue trauma and applying pharmacological and/or barrier adjutants, to decrease adhesion formation and to prevent adhesion by gynecological laparoscopic surgery.

Yu. Asherman syndrome. Fertil Steril 2008.

Fig. 1: Hysteroscopic view of a case of Asherman syndrome with adhesions bands in the anterior and left lateral side wall of the uterine cavity

**Surgical Technique:** Laparoscopy has been thought to have an advantage of reducing the formation of post-operative adhesions, as it seems to meet most of the well-known principles of a traumatic, gentle and bloodless surgery originally described. Laparoscopy with its minimal access to the abdominal cavity reduces the amplitude of peritoneal injury, which seems to play a pivotal role in the pathophysiology of adhesion formation [18]. Avoiding incisions through highly vascularized anatomical structures, e.g. muscle layers and minimizing the extent of tissue trauma are the two confirmed basic principles for reducing post-operative adhesions. Minimal access also prevents the abdominal cavity from exposure to air and foreign reactive materials, thus reducing the formation of adhesions at locations distant from the operative site [19]. The laparoscopic magnified view enables a gentler handling and a more precise dissection of anatomical structures at the operative site, thus contributing to minimize the degree of tissue trauma. Moreover, recent findings seem to indicate that the laparoscopic environment may reduce post-operative adhesion formation by directly interfering with the fibrinolytic activity of peritoneum via the inhibition of plasminogen activator inhibitor 1 (PAI-1) released by mesothelial cell. Such concepts contrast with conclusions drawn) which have demonstrated that carbon dioxide ($CO_2$) pneumoperitoneum during laparoscopic surgery may act as a cofactor in post-operative adhesion formation mostly by inducing peritoneal hypoxia through a compression of the capillary flow in the superficial peritoneal layers. Furthermore, it has been demonstrated that $CO_2$ pneumoperitoneum induces respiratory acidosis that, if not corrected, leads to metabolic acidosis and metabolic hypoxia. This could be deleterious for the peritoneal cells and enhance the detrimental effect of the $CO_2$ pneumoperitoneum-inducedperitoneal ischaemic hypoxia.( Role of $CO_2$). Further studies have shown that COpneumoperitoneum enhances adhesion formation through an up-regulation of hypoxia inducible factors. (Role of hypoxia inducile factors. 1alpha and 2alpha in basal adhesion formation and in carbon dioxide plasminogen system (PAI-1) members of the vascular endothelial growth factor family and placental growth factor).

Furthermore, a role for reactive-oxygen species (ROS) in post-operative adhesion formation at laparoscopy has been suggested, since ROS is produced during the ischaemia-reperfusion process (insufflation of peritoneum = ischaemia; deflation of pneumoperitoneum = reperfusion) and the administration of ROS scavengers has been demonstrated to decrease adhesion formation. Hypothermia has been demonstrated to reduce the toxic effects of hypoxia and of the ischaemia-reperfusion process in mice [20]. On the other hand, the use of humified gases has been demonstrated to minimize adhesion formation induced by dessication. Thus, the concept of combining controlled intraperitoneal cooling with a rigorous prevention of dessication might be important for clinical adhesion prevention. However, laparoscopic technique, a further improvement in preventing adhesion formation in gynaecologic laparoscopy may be provided by the adherence to ‘good’ surgical techniques, amount of Ringer's lactate at the completion of the procedure should be followed. Modern surgical devices are provided with both cutting and homeostatic activities, thus sparing the use of multiple ligatures, which also favour adhesions. The newly developed laparoscopic techniques, it is worth mentioning, that temporary ovarian suspension is a technique recently proposed as a simple and effective method in preventing periovarian post-operative adhesions, especially in the case of surgery for advanced endometriosis. Less recent are the numerous adjusting in laparoscopic technique proposed to prevent adhesion formation in the case of myomectomy or interventions

for tubal pregnancy. Every gynaecologist performing pelvic surgery by laparoscopic techniques believes that this result in fewer post-operative adhesions than similar procedures performed at laparotomy.

**Pharmacological Adjuvants:** A wide variety of pharmacological adjuvant, including steroidal and non-steroidal anti-inflammatory agents, antihistamines, progesterone, gonadotrophin-releasing hormone (GnRHa) agonists, fibrinolytics and anticoagulants have been tested to prevent post-operative adhesion formation following open abdominal surgery without any clearly demonstrated.

**Anti-Inflammatory Agents:** Progesterone has been investigated for reduction of post-operative adhesions after the initial observation that adhesions were reduced after ovarian wedge resection if that ovary was containing an active corpus luteum at the time of operation. The role of progesterone in preventing post-operative adhesion formation reported exclusively on patients treated by traditional surgery. At present, the use of progesterone in preventing adhesion development in clinical practice is also not recommended. Combined pre-operative and post-operative treatment with GnRH agonists has been shown to decrease adhesion formation and reformation in both animal models and clinical trials. Among the various direct and indirect actions through which GnRH agonists might modulate adhesion formation, the interference with fibrinolytic processes seems to be predominant. On the basis of the data available, adhesion prevention seems to be at its best when pre- (2-3months) and post-operative (2-3 months) GnRH agonists treatment is administered. At present, no studies evaluating the role of GnRH agonists in preventing adhesion following laparoscopic gynaecological procedures are available in the literature.

**Fibrinolytic Agents:** An imbalance between fibrin-forming (coagulation) and fibrin-dissolving (fibrinolytic) activities in the peritoneum has been hypothesized as one of the major pathogenetic factors in adhesion development in animals [21]. A recent prospective study in humans seems to add further weight to the hypothesis that this also applies to humans. Fibrinolytic agents have been suggested in preventing adhesions, as they act directly by reducing the fibrinous mass and indirectly by stimulating plasminogen activator (PA) activity. Thrombolytic agents including plasmin preparations (plasmin, actase and fibrinolysin) and plasmin activators (streptokinase, urokinase and recombinant human tissue PA) have been found to be effective in preventing adhesion formation in the greater part of the reviewed animal and clinical studies. However, the current use of fibrinolytic agents in humans awaits further evaluation of their safety and side effects. Moreover, studies pertaining to the role of fibrinolytic agents on the prevention of adhesion after gynaecological laparoscopic surgery are still missing.

**Anticoagulants:** Heparin is the most widely investigated anticoagulant used for prevention of adhesions. Its mechanism of action may be mediated by an interaction with antithrombin III in the clouding cascade or by a direct stimulation of the activity of PAs. Animal studies where heparin was administered by different routes either alone or in combination with peritoneal irrigants, carboxymethylcellulose instillates or mechanical barriers resulted in conflicting reports demonstrating its efficacy in reducing adhesion formation and reformation. However, the efficacy of heparin in reducing adhesion formation whether administered alone or in combination with Interceded TC7 barrier was not able to be demonstrated in the two clinical trials available in the literature. Also, heparin was found to have no therapeutic advantage over Ringer's lactated solution in the prevention of post-operative pelvic adhesion, in the paper reporting on patients undergoing laparoscopic surgery for different gynaecological conditions.

**Antibiotics:** The rationale behind the use of antibiotics is prophylaxis against infection and hence the inflammatory response that triggers the adhesion formation. Systemic broad-spectrum antibiotics, particularly cephalosporins, were widely used in the past. At present, there is insufficient published data from human studies supporting this practice.The ideal barrier should be noninflammatory, nonimmunogenic, persist during the remesothelialization, stay in place without suture, remain active in the presence of blood and be completely biodegradable.

**Oxidized Regenerated Cellulose:** Oxidize regenerated cellulose (ORC), the most widely used adhesion-reducing substance and has been shown human studies (on the) Use of Interceded (TC7) absorbable adhesion barrier

to reduce Post-operative adhesion reformation in infertility and endometriosis surgery. To reduce adhesion formation by its transformation into a gelatinous mass covering the damaged peritoneum and forming a barrier physically separating adjacent raw peritoneal surfaces. The use of ORC was associated with a reduced incidence of both de novo and reformed adhesions as diagnosed at the second-look laparoscopy. In the first study, reported a significant reduction of de novo adhesion formation in premenopausal women undergoing laparoscopic myomectomy with the application of ORC on the uterine incisions and sutures, in comparison with those undergoing the same surgery but without any specific antiadhesive strategy.

**Expanded Polytetrafluoroethylene:** Expanded polytetrafluoroethylene non-absorbable barrier has also undergone evaluation in a randomized multicentre controlled trial. This product must be sewn in place and is usually removed during a second surgical procedure. In patients undergoing gynaecological surgery by laparotomy for adhesions or myoma, Gore-Tex Surgical Membrane was shown to decrease the severity, extent and incidence of adhesions in treated areas. Its usefulness is limited by the nature of the product: it must be sutured in place and, in most cases, should be removed at a subsequent surgery. It is very difficult to apply at laparoscopy.

**Icodextrin:** Icodextrin (ADEPT, Baxter, USA) is an $\alpha$-1, 4 glucose polymer of high molecular weight, which is rapidly metabolized to glucose by the $\alpha$-amylase in the systemic circulation, but is adsorbed only slowly from the peritoneal cavity. The 4% solution of icodextrin, having a longer peritoneal residence time ($\geq$4 days) than crystalloid solutions has the potential to significantly reduce post-surgical adhesion formation by means of a prolonged hydroflatation.

**Hyaluronic Acid:** Hyaluronic acid (HA) is a naturally occurring glycos aminoglycan and a major component of the extracellular matrix, including connective tissue, skin, cartilage and vitreous and synovial fluids. This polymer is biocompatible, nonimmunogenic, non-toxic and naturally bioadsorbable. Intraperitoneal instillation coats serosal surface minimizes serosal dessication and reduces adhesion formation. However, its use after tissue injury is ineffective. Cross-linking HA with ferric ion (FeHA) increases the viscosity and half-life. In a large multicentre randomized study showed that Intergel. The first marketed derivative of FeHA, was effective in reducing the extension and the severity of post-operative adhesions in comparison to lactated Ringer's solution in patients undergoing peritoneal cavity surgery by laparotomy with a planned second-look laparoscopy. Likewise, in three other randomized trials ferric hyaluronate gel was demonstrated to be safe and highly efficacious in reducing the number, severity and extent of adhesions throughout the abdomen following pelvic laparotomic surgery. Further, the application of ACP as an antiadhesive barrier in infertile patients undergoing laparoscopic myomectomy is associated with the increased pregnancy rates than laparoscopic myomectomy alone. The favourable safety profile and the efficacious antiadhesive action of this adjunct following laparoscopic myomectomy have been recently confirmed in a blinded, controlled, randomized, multicentre study.

**Solution of HA:** Sepracoat coating solution a liquid composed of 0.4% sodium hyaluronate (hyaluronic acid) in phosphate buffered saline is applied intraoperatively, prior to dissection, to protect peritoneal surfaces from indirect surgical trauma or post-operatively to separate surfaces after they are traumatized [22]. In humans, preliminary results were promising and have been confirmed in a multicentre randomized trial where intraperitoneal Sepracoat instillate was safe and significantly more effective than placebo in reducing the incidence, extent and severity of de novo adhesions to multiple sites indirectly traumatized by gynaecologic laparotomic surgery [23].

**Viscoelastic Gel:** Oxiplex/AP Gel is a viscoelastic gel composed of polyethylene oxide and carboxymethylcellulose stabilized by calcium chloride specifically formulated for laparoscopic application, with tissue adherence and persistence sufficient to prevent adhesion formation.

**Hydrogel:** SprayGel consists of two synthetic liquid precursors that, when mixed, rapidly cross-link to form a solid, flexible, absorbable hydrogel. The solid polymer acts as an adhesion barrier and it can be easily applied by laparoscopy. The currently available evidence does not support the use of SprayGel either in decreasing the extent of adhesion or in reducing the proportion of women with adhesions.

**Prevention of IUA in Hysteroscopic Surgery**

**Surgical Technique:** As for hysteroscopic, the adherence to an appropriate hysteroscopic surgical technique may minimize the risk of post-operative IUA. General recommendations include avoiding trauma of healthy endometrium and myometrium surrounding the lesions to be removed and reducing the usage of electrosurgery whenever possible especially during the removal of myomas with extensive intramural involvement and avoiding forced cervical manipulation.

**Early Second-Look Hysteroscopy:** An early second-look hysteroscopy after any hysteroscopy surgery has been advocated as an effective preventive and therapeutic strategy. Indeed, although IUAs are recognized, they are likely to be 'mild' and they can be easily dissected by hysteroscope sheath alone or by micro scissors. However, the relevance of removing 'mild' intracavitary adhesions has not yet been proven.

**Antibiotic Administration:** Antibiotic administration before, during and after hysteroscopic surgery to avoid infections and therefore to prevent post-operative IUA is not consistently recommended.

**Pre-Operative Hormonal Endometrial Suppression:** GnRH analogues and danazol are widely administrated before some major hysteroscopic procedures (e.g. transcervical resection of endometrium, myomectomy and metroplasty) to provide technically optimal conditions for the surgery (by suppressing the endometrium and by decreasing vascularity and oedema), as well as to minimize perioperative complications (perforation, fluid overload and bleeding). The role of endometrial suppression before resectoscopic surgery on the frequency of post-operative IUA has been questioned.

**Post-Operative Hormonal Treatment:** The post-operative administration of conjugated oestrogen (dose: 1.25-5 mg daily) for 30-60 consecutive days and progestin therapy in a cyclic regimen seem to stimulate the endometrium so that the scarred surfaces are re-epitheliazed. However, the efficacy of this method needs to be validated by large randomized studies. The insertion of a levonorgestrel-releasing intrauterine device (IUD) might represent another promising tool to prevent IUA adhesions, but studies addressing this issue are still missing.

**Barrier Methods:** The maintenance of the freshly separated uterine cavity after any uterine forced intervention is an essential prerequisite for prevention of subsequent adhesion formation, whereas rapid endometrial re-growth might be enhanced by oestrogen and progestogens cyclic administration [24].

**Intrauterine Device:** For several years, the placement of an IUD in the uterine cavity for1- 3 months has been considered the standard method of maintaining the uterine cavity after uterine forced intervention [24]. However the specific type to be used for this purpose remains a controversial issue. The copper-bearing IUDs and the progestasert intrauterine system (IUS) seem to have a too small surface area to prevent adhesion reformation, whereas those containing copper might induce an excessive inflammatory reaction. Actually, the loop-IUS seems to represent the best to use as it keeps the raw dissected surfaces separated during the initial healing phase, reducing the chance of re-adherence. Despite good results, this method has been associated with several complications such as infections, uterine perforation and misplacement of the device and IUA recurrence. Prophylactic antibiotics are recommended to minimize the risk of infection.

**Foley Catheter Balloon:** An inflated pediatric Foley catheter balloon inserted into the uterine cavity for several days retains separation of the uterine walls with fewer complications in comparison with IUDs Fig. 2 [24].

Fig. 2: Foley catheter balloon

Its use is however limited because of the need for hospitalization during the duration of treatment, pain and the shortness of the treatment period which, in itself, is an obstacle in ensuring definitive results in preventing IUA [15]. Foley catheter is not only safe but also effective in the restoration of normal menstrual pattern and fertility.

**Auto-Cross-Linked HA Gel:** The introduction of APC gel into the uterine cavity at the end of the hysteroscopic surgery is through the out-flow channel of the resectoscope, whereas the surgeon progressively limits the entering of the distension medium through the in-flow channel. The procedure is considered complete when, under hysteroscopic view, the gel seems to have replaced the entire liquid medium and the cavity appears completely filled by the gel from tubal osthia to internal uterine orifice. Its high viscosity and adhesiveness makes it easier to introduce the gel into the uterine cavity and ultrasound scans have confirmed that ACP gel remains in situ for at least 72.

**HA and Carboxymethylcellulose Barrier:** Seaprafilm is a bioresorbable membrane of chemically modified HA and carboxymethylcellulose, which has been shown to be effective in reducing adhesion formation after suction curettage for incomplete and missed abortion.

## DISCUSSION

The extent of scar formation is critical. Small scars can usually be treated with success either pharmacological agents (anti-inflammatory, antioxidants, anticoagulants and fibrinolytics) [25] or physical barriers, where substances are interposed between adjacent injured surfaces to avoid direct contact after surgery. Extensive obliteration of the uterine cavity or fallopian tube openings (Ostia) may require several surgical interventions or even be uncorrectable. In this case surrogacy, IVF or adoption may be advised. Patients who carry a pregnancy after correction of Asher man's syndrome may have an increased risk of having abnormal placenta ion including placenta accrete where the placenta invades the uterus more deeply, leading to complications in placental separation after delivery. Premature delivery, second-trimester pregnancy loss and uterine rupture other reported complications. They may also develop incompetent cervix where the cervix can no longer support the growing weight of the fetus and the pressure causes the placenta to rupture and the mother goes into premature labour. Cerclage is a surgical stitch which helps support the cervix if needed. Age is another factor contributing to fertility outcomes after treatment of Asherman's. For women under 35 years of age treated for severe adhesions.

## CONCLUSIONS

Although minimally invasive endoscopic approach has been shown to be less adhesiogenic than traditional surgery, it does totally eliminate the problem. Many attempts have been made to further reduce adhesion formation following endoscopic procedures and many surgical techniques; pharmacological agents and mechanical barriers have been advocated to address this issue.

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