

# Adhesion prevention in gynecologic surgery

Togas Tulandi and Abdulaziz Al-Shahrani

## Purpose of review

The purpose of this review is to discuss new substances and techniques to prevent post-surgical adhesion formation.

## Recent findings

Intraperitoneal administration of sprayable hydrogel and hyaluronic acid appears to decrease postmyomectomy adhesions. Intrauterine instillation of auto-crosslinked hyaluronic acid is associated with fewer intrauterine adhesions. Temporary abdominal oophoropexy after surgery of stage III and IV endometriosis might be beneficial in reducing ovarian adhesion.

## Summary

There has been a wide range of adhesion-reducing substances evaluated in animal models. However, in clinical situations, no adhesion-preventing substance, material, or barrier is unequivocally effective. In view of surgical technique, compared to laparotomy, the laparoscopic approach is associated with less adhesion formation. Temporary abdominal oophoropexy may provide a promising technique to prevent ovarian adhesions. Future research should also be directed toward preventing intrauterine adhesions.

## Keywords

adhesion, adhesion prevention, gynecologic surgery, laparoscopy

## Introduction

One of the complications of abdominal surgery is intra-abdominal adhesion formation. These adhesions can cause bowel obstruction and pain, whereas adnexal adhesions can cause infertility [1]. In an attempt to decrease adhesion formation, many surgical techniques have been proposed and many adhesion-reducing substances have been evaluated. Muzii [2\*\*] conducted a postal survey among 42 members of the Roman Group of Gynecologic Endoscopy in Italy on the use of substances for postoperative adhesion prevention. Approximately two-thirds of the respondents used some method of adhesion prevention. Prophylactic antibiotics were used by 87.5% of respondents. The most frequently used method during laparoscopy was Ringer's lactate, followed by ferric hyaluronate gel. Ringer's lactate is rapidly absorbed from the peritoneal cavity and in humans is ineffective.

In this review, we will summarize recent studies on techniques and adhesion-reducing substances.

## Adhesion-reducing substances

There has been a wide variety of adhesion-reducing substances evaluated in animal models and in humans. Some are pre-existing products or their modifications and others are new substances.

## Hyaluronic acid

Hyaluronic acid is a high-molecular-weight polymer that under aqueous physiologic conditions forms a highly viscous solution. This polymer is present during embryogenesis and it may be responsible for healing without scar formation after fetal surgery.

Intraperitoneal instillation of hyaluronic acid coats serosal surfaces, minimizes serosal desiccation and reduces adhesion formation. Unlike other peritoneal instillates, it should be instilled before trauma is inflicted. Its use after tissue injury is ineffective.

In a small study of 18 women who underwent myomectomy by laparotomy, hyaluronic acid was used [3]. Pelvic adhesions were encountered in five patients (27.7%). The authors commented that their study emphasized the need to improve treatments for adhesion prevention.

## FeHA

Crosslinking hyaluronic acid with ferric ion (FeHA) increases its viscosity and half-life. The first marketed

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Department of Obstetrics and Gynecology, McGill University, Canada

Correspondence to Togas Tulandi MD, Professor of Obstetrics and Gynecology, Milton Leong Chair in Reproductive Medicine, McGill University, Canada, 687 Pine Ave. West, Montreal, Quebec, Canada H3A 1A1  
Tel: +1 514 934 1934 ext. 31391 or +1 514 340 8222 ext. 4920;  
fax: +1 514 843 1448; e-mail: togas.tulandi@mcgill.ca

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derivative of FeHA is Intergel (Lifecore, Johnson and Johnson Gynecare Unit, Medical, New Brunswick, NJ, USA). The gel is supplied in a single-use bottle. In a large multicenter randomized study, Johns *et al.* [4] reported that it was effective in reducing adhesions. In an animal model, FeHA does not prevent adhesion formation [5]. The product was withdrawn from the market due to several reports of late-onset postoperative pain requiring repeated surgery. Other reported side effects are foreign-body reactions and tissue adherence.

#### *Auto-crosslinked hyaluronic acid*

Modifying hyaluronic acid to obtain an auto-crosslinked hyaluronic acid increases its adhesivity and prolongs its residence time on injured raw surfaces. In a small study, this substance was found to decrease postmyomectomy adhesion formation [6]. The authors also noted that subserous suture was associated with less adhesion than interrupted figure-of-eight sutures.

Guida *et al.* [7\*\*] found that intrauterine application of this agent after hysteroscopic surgery is associated with fewer intrauterine adhesions. Indeed, intrauterine adhesions can cause infertility and miscarriage. Currently, the degree of interest in preventing intrauterine adhesion formation and reformation is still not high.

#### *Combined hyaluronic acid and carboxymethylcellulose (HAL-C)*

Sepracoat (HAL-C, Bioresorbable Membrane; Genzyme Corporation, Cambridge, MA, USA) is composed of chemically derived sodium hyaluronate and carboxymethylcellulose. It coats serosal surfaces and is absorbed from the peritoneal cavity within 7 days. Kelekci *et al.* [8] recently confirmed that it is effective in reducing adhesion in a rat uterine horn model. They also noted less vascularization in the treated group. In a multicenter randomized study, Diamond [9] reported that Sepracoat decreases *de novo* adhesion formation.

A slight modification of the peritoneal instillate Sepracoat is the bioresorbable membrane Seprafilm (Genzyme Corporation), supplied in 12.7 × 15.2 cm sheets. It was reported to be effective in reducing the incidence, extent, and severity of postmyomectomy adhesions [10].

#### **Hydrogel (Spraygel)**

One of the novel techniques of substance delivery into the abdominal cavity is by combining two streams of liquid polymers, delivered via catheter to the target tissue. The combination of these polymers produces solid polymer in a few minutes. Using this technique, sprayable hydrogel was developed (Spraygel; Confluent Surgical, Boston, MA, USA). It can be applied easily by laparoscopy. The solid polymer acts as an adhesion barrier and can potentially serve as a carrier for localized

delivery of drugs. In a randomized study, Mettler *et al.* [11•] evaluated 66 women who underwent myomectomy with or without Spraygel application. A second-look laparoscopy was performed in 40 women. They reported that seven of 22 patients (31.8%) in the Spraygel group and two of 18 patients (11.1%) in the control group were free of adhesions. The power of the study was low and the authors did not subgroup patients to laparoscopic myomectomy or myomectomy by laparotomy.

#### **Viscoelastic gel**

This substance consists of polyethylene oxide and carboxymethylcellulose stabilized by calcium chloride. In a small randomized series, 15 ml of this substance was instilled to the adnexal area in 25 patients [12]. The results were compared to those of 24 patients who underwent surgery without the use of the gel. The authors reported that viscoelastic gel decreases postsurgical adnexal adhesions. However, they also found that patients with severe adhesions and concurrent stage IV endometriosis did not have a reduction in adhesion score with the use of this substance.

#### **Vitamin E**

Vitamin E has antioxidant, anti-inflammatory, and anti-fibroblastic effects. In addition, it decreases collagen formation. In theory, it may decrease adhesion formation. In a cecal abrasion model, intraperitoneal administration of vitamin E in olive oil was effective in reducing adhesion formation [13•]. Intraperitoneal instillation of olive oil as well as intramuscular administration of vitamin E was ineffective.

#### **Miscellaneous substances**

The following are other substances that have been evaluated for adhesion prevention. To date, only animal studies are available.

#### *Camptothecin-loaded films*

Animal studies have shown that a substance that inhibits inflammation and angiogenesis might be effective in reducing adhesion formation. Camptothecin is a drug with anti-inflammatory, antiproliferative, and antiangiogenic properties. It belongs to a general class of compounds, the topoisomerase inhibitors, that includes antineoplastic drugs such as doxorubicin. The use of crosslinked hyaluronic acid film containing camptothecin was evaluated in a rat cecal sidewall abrasion model [14]. Adhesion formation was decreased in the treated rats. No toxicity was observed. Whether this substance is safe for human use is unknown.

#### *Sodium chromoglycate*

Sodium chromoglycate stabilizes the membranes of mast cells. In a rabbit cecal abrasion model, this substance decreases adhesion formation [15]. Addition of aprotinin

and dexamethasone increases its efficacy. Dexamethasone alone has been investigated previously and is clinically ineffective. Aprotinin is a proteolytic enzyme that inhibits kallikrein and plasmin. Its efficacy when used alone has been inconclusive.

#### *Ibuprofen-loaded poly-(L-lactic acid) polyethylene glycol*

Using a vehicle such as polyethylene glycol, an active drug can be delivered to a tissue locally. In a rat model, nonsteroidal anti-inflammatory drug (ibuprofen)-loaded poly-(L-lactic acid) (PLLA) polyethylene glycol (PEG) decreased adhesion formation [16]. Many other substances that have been tried in animal models, but their efficacy remains unclear.

### Modification of surgical technique

Despite the use of laparoscopic technique and the use of microsurgical principals such as gentle tissue handling, use of fine instruments, and non-reactive suture material, postsurgical adhesions are still a problem. Furthermore, to date no adhesion-reducing substance is unequivocally effective. Surgeons are still trying to find a surgical technique that decreases adhesions.

#### Peritoneal closure

Randomized trials on peritoneal non-closure have shown that closing the peritoneum – either parietal or visceral peritoneum – is unnecessary. It is associated with slightly longer operating time, more postoperative pain, and there is a suggestion that it might cause more adhesion formation [17]. Ellis [18] noted that there have been increasing medicolegal claims arising from adhesion-related complications. He stated that ‘peritoneal defects and the pelvic floor should be left open since they rapidly reperitonealized’.

#### Temporary abdominal oophoropexy

In an attempt to prevent ovarian adhesion, several authors have advocated transient abdominal oophoropexy. Ouahba *et al.* [19\*\*] performed this procedure in 20 young women with stage III and IV endometriosis. Ovarian suspension was done using 3-0 Prolene that was inserted on the medial surface of the ovary adjacent to the ovarian ligament, bringing the ovary laterally and apposing the medial surface of the ovary to the anterior abdominal wall. The suture was tied on the low abdominal quadrant and removed 4 days later. Eight patients underwent a second-look laparoscopy and this procedure appeared to be effective. However, a larger study is needed to prove the benefits of this technique.

#### Modification of pneumoperitoneum

In laparoscopic surgery, pneumoperitoneum with CO<sub>2</sub> gas is a necessity. However, it has been suggested that the low temperature of the gas might be associated with more peritoneal injury. This has led to the use of warm gas but

the effects on adhesion formation remain unclear. Instead of modifying the temperature of the pneumoperitoneum gas, Binda *et al.* [20] investigated the effects of room temperature on adhesion formation in a mouse model. Compared to those in a chamber at 37°C, rats kept at 23–25°C had decreased adhesion formation. It is possible that hypothermia decreases the toxic effects of hypoxia and of the ischemia-reperfusion process. Most studies on modifying the temperature, humidity, or consistency of pneumoperitoneum gas are performed with animal models. The implications in humans remain unclear.

### Conclusion

There has been a wide variety of adhesion-reducing substances evaluated in animal models. Among the newest agents are hyaluronic acid and sprayable hydrogel. In a small study, they have been shown to be effective in reducing postmyomectomy adhesions. Surgical approach is an important factor with laparoscopy being associated with less adhesion formation compared to laparotomy. For laparotomy, closure of the peritoneum is unnecessary, and might be associated with more adhesion formation. The recent practice of temporary abdominal oophoropexy after surgery of stage of III and IV endometriosis might be beneficial.

Currently, the degree of interest in preventing intrauterine adhesion formation and reformation is still not high. One study shows that intrauterine application of auto-crosslinked hyaluronic acid decreases intrauterine adhesions.

Today, we are still far from finding the ideal adhesion-preventing agent [21]. There is still no adhesion-preventing substance, material, or barrier that is unequivocally effective. One can reduce the adhesion formation, but not prevent it entirely. Fortunately, we are not alone; other specialists including general surgeons, neurosurgeons, ophthalmologists, and others have become aware of the problem and are actively trying to find the solution.

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