

PERITONEAL ADHESIONS IN GYNAECOLOGICAL SURGERY: THEORY AND EVIDENCE

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Introduction

- Adhesions
 - abnormal attachments between tissues and organs
- Intra-abdominal: congenital or acquired
 - Congenital adhesions
 - Consequence of embryological anomaly in the development of the peritoneal cavity.
 - Acquired adhesions
 - Inflammatory response of the peritoneum that arises after intra-abdominal inflammatory processes.
 - Majority of acquired adhesions (about 90%) are post-surgical

Acquired adhesions

- Inflammatory factor:
 - tissue trauma, infection, ischaemia, foreign body's reaction (sutures, powder from gloves, gauze particles), haemorrhage, tissue overheating or drying and exposure to irrigation fluids
- Symptoms:
 - Asymptomatic
 - Intestinal obstruction
 - Chronic pelvic or abdominal pain
 - Female infertility

Mechanism of adhesion development

- Peritoneal healing- what differs from other tissue
 - Process:
 - Metaplasia, migration and proliferation
 - Healing time:
 - Regardless of their size

Mechanism of adhesion development

- Peritoneal healing & adhesion formation
 - Same for the first 3 days after peritoneal injury.
 - Peritoneum injuries
 - Disruption of stromal mast cells
 - Release of histamine and vasoactive cinins
 - Cytokine released
 - Attract and activate macrophages → vasodilating substances → capillary permeability ↑ → fibrous exudate formation

Mechanism of adhesion development

- Peritoneal healing & adhesion formation
 - Platelets:
 - important component of the inflammatory exudate
 - ability to adhere it to the traumatized surfaces
 - Platelet degranulation
 - Releases adrenaline, transforming growth factor beta and serotonin
 - Contribute to the production of prostaglandins and leukotrienes
 - Fibrin clot
 - Coagulation process

Mechanism of adhesion development

- Peritoneal healing & adhesion formation
 - Activation of the coagulation
 - Inactive prothrombin into thrombin
 - Thrombin triggers the conversion of fibrinogen into monomers of fibrin(interact and polymerize)
 - Initially soluble polymer becomes insoluble by factor XIIIa
 - Fibrinous material (Exudate within 3h) →defective area, generates attachments of adjacent tissue surfaces
 - Blood(bleeding) increases the fibrin deposition
 - Most fibrin depositions disperse by fibrinolysis
 - Fibrinous mass remains, results in the organization and formation of adhesions

Mechanism of adhesion development

- Peritoneal healing & adhesion formation
 - Polymorphonuclear cells, macrophages, fibroblasts and mesothelial cells
 - Migrate and proliferate into the fibrinous exudate
 - Macrophages increase → secrete a variety of substances → recruit mesothelial cells onto the injured surfaces
 - Mesothelial cells form islands, proliferate and cover the injured area
 - Release substances: plasminogen activator, plasminogen activator inhibitor, arachidonic acid metabolites, reactive oxygen species, cytokines, IL-1, IL-6, TNF- α , prostaglandin E2, collagenase, elastase and the transforming growth factors leukotriene B4 alpha and beta (TGF- α and TGF- β) → peritoneal healing and adhesion formation modulation

Mechanism of adhesion development

- Peritoneal healing & adhesion formation
 - Deposition & degradation
 - determine normal peritoneal healing or adhesion formation
 - Fibrin absorption via fibrinolysis
 - Inactive plasminogen is converted to plasmin through tissue plasminogen activator (tPA) and urokinase type plasminogen activator (uPA)

Mechanism of adhesion development

- Peritoneal healing & adhesion formation
 - Fibrin absorption via fibrinolysis
 - tPA
 - Mesothelium and submesothelial blood vessels of serosal and peritoneal membranes
 - Fibrinolytic activity begins at day 3 after peritoneal injury, maximum by day 8
 - Adhesions formed in place by day 8, when mesothelial regeneration has been completed

Mechanism of adhesion development

- Peritoneal healing & adhesion formation
 - Fibrin absorption via fibrinolysis
 - Normal peritoneum → high fibrolytic activity
 - IL-1 and IL-6(inflammatory)
 - →Stimulate epithelial and inflammatory cells to release plasminogen activator inhibitor 1 and 2 (PAI-1 and PAI-2)
 - → Inhibit fibrinolytic activity
 - Overexpression of PAI-1 → adhesion
 - Other factors: decrease fibrinolysis
 - deficient blood supply
 - reduced tissue oxygenation
 - release of reactive oxygen species

Adhesion prevention

□ Surgical techniques

Table 1 Surgical techniques for prevention of adhesion formation.

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- Minimizing surgical trauma
 - Minimizing tissue handling
 - Avoiding peritoneum suturing or use of fine non-reactive suture
 - Achieving excellent haemostasis and avoiding local ischaemia
 - Reducing drying or overheating of tissues
 - Avoiding foreign bodies (talc, starch)
 - Removing intra-peritoneal blood deposits
 - Reducing infection risk
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Adhesion prevention

- Anti-adhesive agents
 - pharmacological agents, systemic or intra-peritoneal
 - intra-peritoneal barriers (solid or liquid)
 - Pharmacological agents (Table 2) target the modification of inflammatory reaction (limitation of fibrin deposition), amplification of fibrin absorption and suppression of fibroblast activity
 - Barriers (Table 3) are used in order to prevent traumatized peritoneal surface apposition during the healing process so as to prevent tissue adherence

Table 2 Pharmacological anti-adhesive agents.

Type	Examples			
Fibrinolytic agents	Fibrinolysin	Anti-inflammatory agents	Corticosteroids Antihistamines Non-steroidal anti-inflammatory drugs Tetracycline Cephalosporin Progesterone Oestrogens Gonadotrophin-releasing hormone agonists Antiproliferative agents Aromate inhibitors Statins Melatonin	
	Papain			
	Streptokinase, streptodornase			
	Urokinase	Antibiotics		
	Hyaluronidase			
	Chymotrypsin, trypsin, pepsin	Other agents		
	Elastase			
	Recombinant tissue plasminogen activator			
	Anticoagulants	Heparin		
		Citrates		
Oxalates				

Table 3 Anti-adhesive barrier methods.

Type	Examples		
Fluid barriers	Various oils Liquid paraffin Amniotic fluid Crystalloid solutions Dextran Icodextrin 4% Polyglycan esters	Exogenous material	Silicone
			Vaseline
			Gelatin
			Metal foils
			Elastic and silk foils
			Expanded polytetrafluoroethylene
Solid barriers (membranes, gel) Endogenous tissue	Omental grafts Peritoneal grafts Bladder strips Fetal membranes		Oxidized regenerated cellulose
			Hyaluronic acid
			Carboxymethylcellulose
			Polyethylene glycol
			Poly lactide
			Fibrin, N,O-carboxymethylchitosan

Laparoscopy and adhesions

- Operative laparoscopy in gynaecology
 - Expectation of reduced adhesion formation
 - A large number of experimental and human clinical trials has shown that laparoscopic surgery is associated with less development of adhesions compared with laparotomy

Laparoscopy and adhesions

- Reduction of adhesion formation by:
 - Minimal tissue handling and trauma
 - Avoidance of exposure to foreign bodies
 - Prevention of tissue drying
 - Increased intra-abdominal pressure → facilitate haemostasis → limits the use of diathermy → ischaemic areas ↓
 - Lower incidence of post-operative infection

Laparoscopy and adhesions

- Pneumoperitoneum with CO₂ might reduced the beneficial effect of laparoscopy in adhesion formation (Binda et al., 2003)
 - Increased intra-abdominal pressure → splanchnic veins flow ↓ → tissue oxygenation ↓ → acidosis and production of reactive oxygen species
 - The clinical impact of reactive oxygen species remains unclear but there is evidence that they are associated with increased adhesion formation.

Pharmacological agents

- Limitation
 - Ischaemia and inadequate blood supply
 - Decrease systemic drug delivery
 - Extremely rapid absorption mechanism of peritoneum
 - ↓ Half life and efficacy of intra-peritoneally administered agents.
 - Anti-adhesion agents must not affect normal wound healing
 - Adhesion formation (fibrinous exudate, fibrin deposition, fibroblast activity and proliferation) has common step of wound healing.

Pharmacological agents

- Non-steroidal anti-inflammatory drugs (NSAID)
 - Modify arachidonic acid metabolism and altering cyclooxygenase activities
 - ↓ Vascular permeability, platelet aggregation, coagulation and enhanced macrophage function
 - A number of locally and systemically administered NSAID have been used in experimental trials
 - No relevant clinical trials in patients undergoing gynaecological surgery

Pharmacological agents

- Non-steroidal anti-inflammatory drugs (NSAID)
 - Questionable efficacy due to rapid absorption from the peritoneal membrane (inadequate concentrations)

Pharmacological agents

- Corticosteroids and antihistamines
 - Corticosteroids ↓ vascular permeability, ↓ cytokine and chemotactic factor secretion → ↓ inflammatory
 - Antihistamines
 - Inhibit fibroblast proliferation
 - Stabilize lysosomal membranes + histamine secretion
 - Corticosteroids alone or plus antihistamines by intra-peritoneal or systemic administration or by flushing through Fallopian tubes post-operatively and were effective in many, but not all, experimental models.

Table 4 Meta-analysis of data from randomized controlled trials in humans assessing the effectiveness of pharmacological agents in adhesion prevention after gynaecological surgery^a

Outcome	No. of studies	Total no. of participants	OR (95% CI)
Non-steroidal anti-inflammatory drugs: no data from RCT			
Corticosteroids (any route) versus no corticosteroids: three RCT (Larsen, 1985; Querleu et al., 1989; Rock et al., 1984)	3	410	1.01 (0.66–1.55) [†]
Deterioration of adhesion score			
Clinical pregnancy			
Post-operative flushing of Fallopian tubes with corticosteroids versus no post-operative flushing: one RCT (Rock et al., 1984)	1	120	0.82 (0.34–1.96) [†]
Clinical pregnancy			
Live Birth	1	120	0.47 (0.11–1.99) [†]
Post-operative corticosteroids in addition to systemic intra-operative steroids versus no post-operative corticosteroids: one RCT (Larsen, 1990)	1	75	0.25 (0.10–0.65) [†]
Deterioration of adhesion score	1	75	4.83 (1.71–13.65) [†]
Improvement of adhesion score			
Antihistamines versus no antihistamines	1	93	0.59 (0.25–1.42) [†]
Deterioration of adhesion score	1	75	0.56 (0.22–1.43) [†]
Improvement of adhesion score			
Progesterone and oestrogens: no data from RCT			
Intra-peritoneal heparin versus no heparin: one RCT (Larsen, 1988)	1	92	1.27 (0.56–2.91) [†]
Deterioration of adhesion score	1	63	0.87 (0.32–2.35) [†]
Improvement of adhesion score			
Heparin plus oxidized regenerated cellulose adhesion barrier versus oxidized regenerated cellulose adhesion barrier alone: one RCT (Reid et al., 1997)	1	40	0.60 (0.24–1.46) [†]
Incidence of adhesions at second-look laparoscopy			
Intra-peritoneal noxytoline versus no noxytoline: one RCT (Querleu et al., 1989)	1	87	0.55 (0.17–1.76) [†]
Deterioration of adhesion score	1	126	0.66 (0.30–1.47) [†]
Improvement of adhesion score			
Clinical pregnancy			
Fibrinolytic agents, antibiotics and other pharmacological agents: no data from RCT			

RCT = randomized controlled trial.
† Not significant.

^a Significant.

Pharmacological agents

- Corticosteroids
 - Adverse events:
 - Pituitary–adrenal axis suppression
 - Immunosuppression
 - Delayed wound healing
- Antihistamines
 - Only one RCT has evaluated the role of oral promethazine in the prevention of adhesion formation after pelvic surgery.
 - In that study, no significant difference was detected either in deterioration or improvement of adhesion score in patients who received promethazine as compared with those who did not.

Pharmacological agents

- Progesterone
 - ▣ Less adhesion formation in animal models
 - ▣ Not appear to be effective in humans
- Oestrogens
 - ▣ Associated with increased adhesion formation in animal models
 - ▣ Hypo-oestrogenic state, produced by gonadotrophin-releasing hormone agonists or aromatase inhibitors such as tamoxifen and anastrozole, decrease development of post-operative adhesions in experimental models
 - ▣ This hypothesis, however, has never been tested in humans.

Pharmacological agents

- Anticoagulants – fibrinolytics
 - ▣ Heparin can reduce adhesion formation by inhibition of the coagulation cascade and promotion of fibrinolysis
 - ▣ Intra-peritoneal irrigation
 - Reduce adhesion formation was associated with haemorrhage and delayed wound healing
 - Low-dose heparin irrigation showed no benefit in adhesion reduction

Pharmacological agents

- Anticoagulants – fibrinolytics
 - ▣ Only 1 available RCT
 - ▣ Heparin delivery with oxidized regenerated cellulose failed to demonstrate a superior effect compared with oxidized regenerated cellulose alone
 - ▣ In experimental trials, the combination of carboxymethylcellulose or 32% dextran 70 plus heparin failed to reduce adhesion formation

Pharmacological agents

- Anticoagulants – fibrinolytics
 - ▣ Fibrinolytic agents
 - Streptokinase, elastase and tissue plasminogen activator produced by recombinant DNA techniques (rtPA)
 - Contribute in adhesion prevention directly by reducing the fibrinous mass and indirectly by stimulating plasminogen activator activity

Pharmacological agents

- Anticoagulants – fibrinolytics
 - ▣ The use of carboxymethylcellulose gel and oxidized regenerated cellulose as a carrier to deliver rtPA intra-peritoneally
 - Not associated with a reduction of adhesion formation in animal models (Bothin, 1995; Gehlbach et al., 1994).
 - No relevant RCT evaluating the efficacy of fibrinolytic agents so far.

Pharmacological agents

- Antibiotics
 - ▣ Prophylaxis against post-operative infections and the inflammatory response that leads to adhesion formation.
 - ▣ Peritoneal irrigation with antibiotic solutions does not reduce adhesion formation, while it has been shown that in some cases it may promote them

Other pharmacological regimens

- Apoptin, noxytioline, growth factor inhibitors and modulators, phosphatidylcholine, thiazolidinediones, colchicine and calcium channel blockers, have been utilized in experimental trials.
- The intra-peritoneal administration of noxytioline
 - The only one RCT
 - no significant difference was identified in terms of reduction of adhesions and clinical pregnancy rates in patients who were administered intra-peritoneal noxytioline and the control group
- There is no data from RCT to support the conclusion that any of the other agents is efficacious in preventing the development of post-operative adhesions

Anti-adhesive barriers

- Keep traumatized peritoneal surface separated during mesothelial regeneration
- Precluding adherence of adjacent organs and tissues and reducing the development of adhesions.
- The separation can be achieved by the use of solid (films or gels) or fluid barriers

Anti-adhesive barriers

- Currently the most useful adjuvant
- Numerous substances (Table 3) have been used as mechanical barriers to separate tissue surfaces
- An anti-adhesive agent should be effective, safe, economical and easy to use in both open and laparoscopic surgery

Anti-adhesive barriers

- Cochrane reviews:
 - The clinical effectiveness of several of these agents has been evaluated
- The corresponding results from these reviews are also reported in brief here.
- In all cases, a separate search in MEDLINE, CENTRAL and EMBASE electronic databases was performed during November 2009 in order to retrieve any additional RCT published up to 2009 and update the pooled results accordingly. These results are presented in Table 5.

Solid barriers

- Providing a separation over one or between two traumatized surfaces
- They are often ineffective in the presence of blood, have a complex preparation and application.
- Do not conform easily to the shape of pelvic organs, need suturing and are difficult to use via laparoscopic surgery.

Solid barriers

- Limited benefits
- Not prevent the development of adhesions at sites of indirect trauma.
- The surgeon has to surmise where adhesions will be formed in order to choose the placement sites and optimize barrier efficacy

Expanded polytetrafluoroethylene

- Expanded polytetrafluoroethylene is a non-absorbable, non-reactive, synthetic material that inhibits cellular migration and tissue adherence.
- In the only available RCT, it has been shown to be associated with fewer post-operative de-novo adhesions after myomectomy when compared with no treatment

Expanded polytetrafluoroethylene

- Preclude was found to be more effective in terms of adhesion reformation after adhesiolysis
- In another RCT, no evidence of a beneficial effect of Preclude was demonstrated in the de-novo formation of adhesions after laparoscopic myomectomy when compared with oxidized regenerated cellulose

Expanded polytetrafluoroethylene

- Must be sutured in place
- Difficult to use in laparoscopic
- Requires a subsequent surgical procedure for removal after the injury has healed
- The use of Preclude in Europe is limited and it has been withdrawn from the market in USA after the development of the absorbable barriers

Oxidized regenerated cellulose

- Fast degradable barrier
- Modification of its precursor Surgicel, which has been used as a haemostatic agent for a long time
- Mesh designed to be placed over or between traumatized surfaces.
- About 8 h after the application in the peritoneal cavity, it becomes a viscous gel and finally it is degraded to monosaccharides and completely absorbed in about 2 weeks
- Oxidized regenerated cellulose use in laparoscopic surgery is feasible

Oxidized regenerated cellulose

- A meta-analysis of 11 relevant RCT (Ahmad et al., 2008) has shown that the barrier is safe and reduces significantly the incidence of de-novo adhesions, as well as the reformation of adhesions as compared with no treatment in laparoscopy

Oxidized regenerated cellulose

- Significant reduction in the reformation (or mixture) of adhesions in laparotomy
- Demonstrated that can be expected with the use of oxidized regenerated cellulose as compared with the no treatment group.

Oxidized regenerated cellulose

- The product is site specific
 - ▣ the efficacy is limited to surgical situations where raw surfaces can be completely covered with the mesh and its benefit is limited to the site of barrier placement.
 - ▣ The fundamental disadvantage is that it becomes ineffective when the entire area is not completely haemostatic.
 - ▣ The presence of small amounts of blood in the peritoneal cavity or post-operative bleeding results in blood permeating the mesh, fibrin deposition and, finally, adhesion formation

Oxidized regenerated cellulose

- Combination of oxidized regenerated cellulose plus heparin resulted in a significant reduction of adhesion formation and reformation in experimental models.
- This improvement in efficacy was not confirmed in clinical trials.

Hyaluronic acid

- Linear polysaccharide with repeating disaccharide units
 - ▣ Composed of sodium D-glucuro-nate and N-acetyl-D-glucosamine.
 - ▣ A naturally occurring component of many body tissues and fluids, where it provides mechanically protective and physically supportive roles
 - ▣ Various combinations of HA have been used for the prevention of adhesion formation.

Hyaluronic acid

- HA and carboxymethylcellulose is an absorbable membrane
 - ▣ Dissolves and forms a hydrophilic gel approximately 24 h after placement
 - ▣ Site-specific barrier and acts by separating mechanically opposite tissue surfaces and lasts for 7 days.
 - ▣ Completely cleared :4 weeks
 - ▣ Absorption of carboxymethylcellulose is not well known
 - ▣ It does not conform to the shape of pelvic organs as well as oxidized regenerated cellulose and is usually used to prevent adhesions between the incision of anterior abdominal wall and bowel or omentum

Hyaluronic acid

- HA and carboxymethylcellulose
 - ▣ In a blind prospective, randomized, multicentre study, the treatment of patients after myomectomy with Seprafilm significantly reduced the extent and area of post-operative uterine adhesions (Diamond, 1996).
 - ▣ Potential side effects
 - foreign body reaction
 - pulmonary emboli
 - intra-peritoneal abscess formation
 - these findings were not statistically significant in the relevant trials

Hyaluronic acid

- HA and carboxymethylcellulose
 - ▣ High cost is another limitation because, for an effective protection from intestinal obstruction, a mean of 4.5 sheets per patient is required (Trew, 2006)

Hyaluronic acid

- Ferric hyaluronate 0.5% gel
 - ▣ viscous gel that provides a broader coverage than previous site-specific agents
 - ▣ shown to be easy to use in open and laparoscopic surgery.
- In relevant prospective randomized trials
 - ▣ Significant reduction of severity and extent of post-operative adhesions
 - ▣ Statistically significant improvement of the American Fertility Society (AFS) and modified AFS scores at second-look laparoscopy

Hyaluronic acid

- It was withdrawn from the market in 2003 because of problems with late onset post-operative pain and rare reports of sclerosing peritonitis

Hyaluronic acid

- Low-viscosity 0.04% HA combined with phosphate-buffered saline
 - ▣ bioabsorbable macromolecular dilute solution of HA that is cleared from the body in less than 5 days.
 - ▣ Applied in the peritoneal cavity before any tissue manipulation in order to protect peritoneal surfaces from indirect trauma and finally before the end of the procedures

Hyaluronic acid

- Low-viscosity 0.04% HA
 - ▣ Statistically significant reduction of adhesions, as well as of the mean adhesion score, at second-look laparoscopy.
- Not effective in reducing post-operative adhesion formation at sites of direct surgical trauma.

Hyaluronic acid

- HA cross-linked to HA
 - ▣ Site-specific highly viscous gel
 - ▣ Easy to use in laparoscopic and open surgery
- In a prospective, randomized, controlled study
 - ▣ rate of post-surgical adhesions after laparoscopic myomectomy was examined
 - ▣ resulted in significantly more adhesion-free patients.
- Pregnancy rates at 6 and 12 months after laparoscopic myomectomy were significantly higher in patients treated with cross-linked HA

Hyaluronic acid

- In another randomized trial, adhesion-free patients after laparoscopic myomectomy were greater in the treatment group but the difference was not statistically significant.
- The incidence and severity of adhesions was similar in both groups, but a significant reduction of uterine adhesions was found in the treatment group

Hyaluronic acid

- When the data from the two aforementioned studies were combined, a statistically significant reduction of adhesions during second-look laparoscopy was detected in the group of patients treated with HA-cross-linked HA as compared with the control group (Table 5).

Table 5 Meta-analysis of data from randomized controlled trials in humans assessing the effectiveness of barrier agents (fluid or solid) in adhesion prevention after gynaecological surgery.

	Outcome	No. of studies	Total no. of participants	OR or WMD (95% CI)
Solid barriers	Expanded polytetrafluoroethylene			
	Gore-Tex versus no treatment: one RCT (Myomectomy ASG, 1995)			
	Incidence of adhesions: de novo	1	42	0.21 (0.05–0.87) [§]
	Expanded polytetrafluoroethylene (Gore-Tex) versus oxidized regenerated cellulose (Interceed): two RCT (Honey et al., 1995; Korell, 1994)			
Oxidized regenerated cellulose	Incidence of adhesions: de novo	1	38	0.94 (0.26–3.36) [§]
	Incidence of adhesions: reformation (or mixture)	1	23	0.16 (0.03–0.80) [§]
	Oxidized regenerated cellulose (Interceed) versus no treatment (laparoscopy): five RCT (Kockstein et al., 1995; Mais et al., 1995a; Mais et al., 1995b; Saravelos and Li, 1995; Walwiener et al., 1998)			
	Incidence of adhesions: de novo	2	75	0.31 (0.12–0.79) [§]
	Incidence of adhesions: reformation (or mixture)	3	100	0.19 (0.09–0.42) [§]
	Oxidized regenerated cellulose (Interceed) versus no treatment (laparoscopy): six RCT (Azziz, 1993; Franklin, 1995; Li and Coome, 1994; Nordic APSC, 1995; Sekita, 1992; van Geldorp, 1994)			
Incidence of adhesions: reformation (or mixture)	6	554	0.39 (0.28–0.55) [§]	

Hyaluronic acid

Hyaluronic acid and carboxymethylcellulose (Sefraprim) versus no treatment: one RCT (Diamond, 1998)			
Extent of adhesions	1	127	-0.45 (-0.76 to -0.14) [§]
Area of adhesions (mm ²)	1	127	-5.5 (-10.09 to -0.91) [§]
Ferric hyaluronate 0.5% gel (Intergel) versus no treatment: two RCT (Johns et al., 2001; Lunderoff et al., 1991)			
Proportion of adhesions at second-look laparoscopy	2	342	0.36 (0.19–0.67) [§]
Deterioration of adhesion score	2	342	0.28 (0.12–0.66) [§]
Improvement of adhesion score	2	342	1.55 (0.82–2.92) [§]
Low-viscosity 0.04% hyaluronic acid (Sepracoat) versus no treatment: one RCT (Diamond, 1998)			
Proportion of adhesions at second-look laparoscopy	1	245	0.32 (0.12–0.89) [§]
Mean adhesion score	1	245	-1.85 (-2.15 to -1.55) [§]
Hyaluronic acid cross-linked to hyaluronic acid (Hyalobarrier) versus no treatment: two RCT (Mais et al., 2006; Pellicano et al., 2005)			
Proportion of adhesions at second-look laparoscopy	2	79	0.25 (0.10–0.63) [§]
Hyaluronic acid cross-linked to hyaluronic acid (ACP gel) versus no treatment: two RCT (Acunzo et al., 2003; Guida et al., 2004)			
Proportion of adhesions at second-look laparoscopy	2	216	0.34 (0.16–0.69) [§]
Cross-linked thio-modified hyaluronic acid with 4% poly(ethylene glycol) diacrylate: no data from RCT			

Table 5 (continued)

	Outcome	No. of studies	Total no. of participants	OR or WMD (95% CI)
Polyactide	Polyactide: No data from RCT			
	Polyethylene glycol (Spraygel) versus polyethylene glycol: one RCT (Mettler et al., 2004)			
	Deterioration of adhesion score	1	40	0.27 (0.05–1.50) [§]
	Improvement of adhesion score	1	31	1.50 (0.12–18.54) [§]
Carboxymethylcellulose	Proportion of adhesions at second-look laparoscopy	1	31	0.18 (0.03–1.06) [§]
	Carboxymethylcellulose and polyethylene oxide (Oxiolext): three RCT (d'Zerega et al., 2007; Lunderoff et al., 2005; Young et al., 2005); meta-analysis of data from these studies was not feasible			
	Fibrin glue (Tissucol): no data from RCT			
	N-(2-carboxymethylchitosan (Adhesix) versus Ringer's solution: one RCT (Diamond et al., 2003); odds ratios or weighted mean differences could not be extracted from this study			
Fluid barriers	32% dextran 70 versus no 32% dextran 70: four RCT (Adhesion Study Group, 1983; Jensen, 1985; Larsson et al., 1985; Rosenberg and Board, 1984)			
	Deterioration of adhesion score	1	166	1.7 (0.66–3.37) [§]
	Improvement of adhesion score	2	210	0.93 (0.46–1.90) [§]
	Proportion of adhesions at second-look laparoscopy	2	268	0.33 (0.18–0.59) [§]
	at second-look laparoscopy			
	Polyglycan esters (Adcon-P): no data from RCT			
	Iodextrin 4% (Adept) versus no Iodextrin 4%: two RCT (Brown et al., 2007; d'Zerega et al., 2002)			
	Deterioration of adhesion score	1	53	0.28 (0.07–1.21) [§]
	Improvement of adhesion score	2	455	1.49 (1.02–2.19) [§]
	Proportion of adhesions at second-look laparoscopy	1	53	0.48 (0.13–1.68) [§]
Incidence of adhesions: de novo	1	402	0.67 (0.45–0.99) [§]	

RCT = randomized controlled trial.
[§]Not significant.
[§]Significant.

Hyaluronic acid

- Auto-cross-linked internal ester form of HA
 - the biocompatibility of the original polymer
 - higher viscosity and extended residence.
 - It is a gel that has been shown to be efficacious in reducing abdominal adhesions in experimental models

Hyaluronic acid

- Two prospective randomized controlled trials have been published so far by the same group regarding the use of ACP gel for the prevention of intrauterine adhesions after hysteroscopic surgery.
 - In these studies, ACP gel has been associated with a significant reduction in the incidence and the severity of subsequent intrauterine adhesions.
 - A stratified analysis of these two studies confirmed this finding by demonstrating a significant reduction in the proportion of patients with adhesions at second-look hysteroscopy (Table 5)

Hyaluronic acid

- Cross-linked thiol-modified HA with 4% polyethyleneglycol diacrylate
 - ▣ a bioabsorbable solution of HA
 - ▣ Carbylan-S is a hydrogel and Carbylan-SX has two formats, a sprayable gel and a hydrogel film
 - ▣ In animal models, Carbylan-S containing mitomycin C and Carbylan-SX were effective in prevention of post-operative intra-abdominal adhesions

Poly lactide

- Bioabsorbable film with a long absorption period (up to 6 months)
- It is metabolized to lactic acid and finally to CO₂ and exhaled through the respiratory system
- It requires suturing in order to avoid its loss from the site.
- In preclinical studies, poly lactide appears to be effective in the reduction of adhesion formation, but there are no data currently for safety and efficacy in humans

Polyethylene glycol

- Synthetic hydrogel formed when two polyethylene glycol-based liquids are sprayed together with an air assisted sprayer at the target tissue, where they cross-link and form a hydrogel barrier.
- One liquid is clear and one is coloured with methylene blue in order that facilitate its application.
- The gel remains intact for approximately 5–7 days and then gradually breaks down by hydrolysis and is cleared through the kidneys (Mettler et al., 2004).
- Drawbacks of the product are the intricacy of preparation and application, the time required to cover the target tissue and the high cost.

Polyethylene glycol

- In a prospective randomized controlled phase-III trial
 - ▣ 40 patients undergoing myomectomy, poly lactide resulted in a significant decrease in the mean tenacity score.
 - ▣ The extent of adhesions was increased in the control group but the difference was not significant.
 - ▣ The proportion of adhesion-free patients at second-look laparoscopy was increased in the treatment group but the difference was not statistically significant
 - ▣ It has been approved for use in laparoscopic and open surgery in Europe, but by the FDA only for use

Carboxymethylcellulose

- Carboxymethylcellulose
- High-molecular-weight polysaccharide
- Derivative of cellulose.
- The mechanism of its absorption is not well known. It has been used in combination with rtPA and with HA

Carboxymethylcellulose

- A composite gel of carboxymethylcellulose and polyethylene oxide is a viscoelastic gel
 - ▣ acts as a barrier between tissues that inhibits protein deposition and thrombus formation
 - ▣ The gel is absorbed by 6 weeks
 - ▣ In cases where large amounts of gel were applied in multiple layers to the surgically treated sites or in cases of stage-IV endometriosis, small collections of gelatinous material were noted in areas of gel application or in areas deep in the cul-de-sac

Carboxymethylcellulose

- In two blind randomized controlled trials, where patients underwent adnexal surgery
 - Carboxymethylcellulose and polyethylene oxide showed a significant improvement of AFS score in the treated group
 - But not in all clinical situations. It did not appear to provide this benefit to patients with grade-IV endometriosis

Carboxymethylcellulose

- Another double-blind prospective randomized controlled trial has shown
 - The mean AFS score for patients in the treatment group was unchanged, while in control patients an increased AFS score was noted.
 - No statistical pooling was feasible for these three studies, since the data were not analysed and presented per randomization unit (they were analysed per adnexa and not per patient).
 - It is easy to use in laparoscopic surgery and it has been approved in Europe for use in abdominal and pelvic surgery

Carboxymethylchitosan

- N,O-carboxymethylchitosan
 - a purified derivative of chitin obtained from the exoskeleton of shrimp and has similar structure to hyaluronic acid and carboxymethylcellulose
 - The product comprises both a clear gel and a solution.
 - The gel is placed initially at the sites of surgical trauma where it is tamped with a laparoscopic instrument and subsequently the solution is placed at the same places.
 - Its efficacy and safety have been confirmed in some animal models.
- A prospective randomized controlled study, performed on 34 patients undergoing laparoscopy for various gynaecological indications
 - decrease in the recurrence, extent and severity of adhesions and a decrease of de-novo adhesion formation at second-look laparoscopy, but none of these findings were statistically significant

Fluid barriers

- Ideal barrier agent because their action is not limited to the site of application.
 - Hydrofloration of intraperitoneal
 - Provides a temporary separation
 - Diluting fibrinous exudates
 - Prevent adhesion formation both at the traumatized area and elsewhere in the pelvis

Fluid barriers

- Side effects
 - leakage from the incision
 - labial oedema
 - Feeling of fluid moving around
 - Abdominal discomfort, distension
 - Complications such as pulmonary and peripheral oedema
 - Large volumes of intra-peritoneal fluids may decrease the peritoneum ability to confront bacterial infections

Crystalloid solutions

- Crystalloid solutions
 - rapidly absorbed by the peritoneal cavity, at a rate of 30–50 ml/h
 - 24 h after the surgery, minimal or no crystalloid solution would be left in the peritoneal cavity.
 - Not seem to decrease adhesion formation
 - Commonly used but they are not approved for use as anti-adhesive agents

Crystalloid solutions

- Used in various combinations (RCT)
 - ▣ Heparin
 - ▣ Steroids
 - ▣ Antihistamines
 - ▣ Other pharmacological
 - ▣ None of them has been found effective in decreasing post-operative adhesion formation or improving pregnancy rates

Dextran

- Dextran
 - ▣ 1–6-linked dextrose polymer.
- A summary (Metwally et al., 2006) of the available data from relevant RCT
 - ▣ Decreased adhesions at second-look laparoscopy in the group that received 32% dextran 70, as compared with the group that did not.
 - ▣ However, despite the fact that the patients with improvement and deterioration in the adhesion score at second-look laparoscopy were increased and decreased respectively, in the treatment group, when compared with the control group, this difference was not statistically significant (Table 5).

Dextran

- Side effects
 - ▣ Pulmonary and peripheral
 - ▣ Liver function abnormalities
 - ▣ Pleural
 - ▣ Allergic reactions
 - ▣ Anaphylactic shock
 - ▣ Disseminated intra-vascular coagulation
 - ▣ It has not been approved for use as an anti-adhesive agent

Polyglycan esters

- Polyglycan esters (Adcon-P; Gliatech, Cleveland, Ohio) is a viscous bioabsorbable solution. Its prototypes Adcon-L and Adcon-T/N were found effective for adhesion prevention in spinal and neurosurgical procedures. Experimental studies have shown that application of Adcon-P effectively reduces development of post-operative intra-abdominal adhesions. There are no data for the safety and the efficacy of this product in humans

Icodextrin

- Icodextrin 4% (Adept ; Shire Pharmaceuticals, Basingstoke, Hampshire, UK) is a 1–4-linked glucose polymer. Icodextrin 4% is a clear isomolar solution and does not predispose to infection. It is absorbed gradually via the lymphatic system into the systemic circulation, where it is digested to oligosaccharides by amylase. Amylase is absent from the human peritoneal cavity. Preclinical studies had shown significant reduction of post-operative adhesions and confirmed the safety of icodextrin 4%. It was indicated that the agent was more effective in adhesion reduction when used as both an irrigant and post-operative instillate

Icodextrin

- In a small double-blind prospective randomized multicentre study, icodextrin 4% resulted in the reduction of incidence, severity and extent of adhesions but these results were not statistically significant (diZerega et al., 2002). However, recently, in the largest prospective randomized double-blind multicentre study for an anti-adhesive agent, icodextrin 4% has been shown to result in a significant reduction of incidence, severity and extent of adhesions and a significant improvement of AFS score. Also the study showed that icodextrin 4% prevents the deterioration of pre-existing adhesions, considering that patients with the higher number of adhesions lysed at initial surgery had the greater reduction in adhesion incidence

Icodextrin

- A stratified analysis of these two studies revealed a statistically significant effect of icodextrin 4% use on the de-novo formation of adhesions, as well as on the proportion of patients with an improvement of the adhesion score at second-look laparoscopy (Table 5).

Icodextrin

- Simultaneously with clinical trials, a European patients registry (ARIEL) was created allowing surgeons to record and report the experiences of the use of icodextrin 4% in open and laparoscopic gynaecological and general surgery.
- The registry provides feedback on routine use in 4620 patients (2882 that underwent gynaecological and 1738 general surgery).
- The general consensus is that it is easy to use in both open and laparoscopic surgery, it is well tolerated by patients and the incidence of adverse events is considered similar to the control group

Icodextrin

- Advantage: Low cost
 - ▣ half the price of each sheet of Interceed or Seprafilm
 - ▣ four times cheaper than one SprayGel package
- Icodextrin 4% has been approved for use in open and laparoscopic surgery in Europe and it was the first anti-adhesive agent that has been approved by the FDA for use in laparoscopic surgery in the USA

Conclusions

- The main strategy to avoid formation and reformation of adhesions
 - ▣ Careful surgical techniques
 - ▣ Anti-adhesive agents
- A wide variety of adjuvants has been used in attempts to prevent adhesion formation
 - ▣ Currently, no single adhesion-preventing agent seems to be unequivocally effective

Conclusions

- Limited evidence from randomized clinical trials support the beneficial effect of most of the barrier agents
- while only post-operative corticosteroids in addition to systemic intra-operative corticosteroids have been found to be useful in the prevention of adhesions after gynaecological surgery
- However, the evidence is not adequate for definite conclusions to be drawn, either in terms of efficacy or in terms of safety, and, thus, further research in this field is warranted.