Chapter 4

Adhesion Prevention Strategies in Laparoscopic Surgery

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http://dx.doi.org/10.5772/52694

1. Introduction

Adhesions are defined as abnormal attachments between tissues and organs [1]. Intra-abdominal adhesions may be classified as congenital or acquired [2]. Congenital adhesions are a consequence of embryological anomaly in the development of the peritoneal cavity. Acquired adhesions result from the inflammatory response of the peritoneum that arises after intra-abdominal inflammatory processes (e.g. acute appendicitis, pelvic inflammatory disease, exposure to intestinal contents and previous use of intrauterine contraceptive devices), radiation and surgical trauma [3]. It has been reported that the majority of acquired adhesions (about 90%) are post-surgical [2].

Factors associated with the formation of post-surgical adhesions include tissue trauma, infection, ischaemia,reaction to foreign bodies (sutures, powder from gloves, gauze particles etc.), haemorrhage, tissue overheating or desiccation and exposure to irrigation fluids [4]. The incidence of intra-abdominal adhesions ranges from 67% to 93% after general surgical abdominal operations and from 60% to 90% after gynecological procedures. Not unexpectedly, adhesion formation is considered one of the most common post-operative complications [2,5]. Post-surgically, many adhesions may be asymptomatic or can lead to a broad spectrum of clinical problems, including intestinal obstruction, chronic pelvic or abdominal pain and female infertility, requiring re-admission and often additional surgery, while at the same time they can complicate future surgical procedures [6]. Adhesion-related re-operations are a common consequence of gynecological procedures and adhesiolysis is followed by a high incidence of adhesion reformation and *de-novo* adhesion formation [7].

The major strategies for adhesion prevention in gynecological surgery aim at the optimization of surgical technique and use of adhesion-prevention agents. Laparoscopic surgery in

gynecology represents the most innovative surgical approach, compared with laparotomy since it has been shown from a large number of clinical, but also experimental studies, that is associated with less development of *de novo* adhesions. Without any doubt, the most important factor is the operating surgeon, whose attention to proper surgical technique will serve as a mainstay for adhesion formation.

2. Mechanism of adhesion development

The mechanism of adhesion formation represents a variation of the physiological healing process [8]. The process of peritoneal healing differs from that of other tissues. Peritoneal defects heal by a process of metaplasia from the underlying mesenchyme, partly from migration of epithelial cells from the free peritoneal fluid and minimally through proliferation of epithelial cells from the defect's edges. Consequently, peritoneal wounds need the same time to heal regardless of their size, in contrast with other tissues, such as the skin, where large injuries take longer to heal than do small injuries [9]. There is no difference between peritoneal healing and adhesion formation for the first 3 days after peritoneal injury. Injuries to the peritoneum cause a disruption of stromal mast cells, resulting in the release of histamine and vasoactive cinins. Also as a response to trauma, various cytokines, such as interleukin (IL)-1, IL-6 and tumor necrosis factor-a (TNF-a) are locally released. The cytokines attract and activate macrophages to secrete vasodilating substances, which in turn, cause an increase in capillary permeability, leading to the formation of fibrous exudate [10]. Platelets are an important component of the inflammatory exudate and have the ability to adhere it to the traumatized surfaces. The platelet degranulation releases adrenaline, transforming growth factor b and serotonin and contribute to the production of prostaglandins and leukotrienes. The chemokines direct the migration of cells to the injury site, while platelets contribute to the initial fibrin clot and to the initiation of the coagulation process [11]. The activation of the coagulation cascade leads to the transformation of the inactive prothrombin into thrombin that triggers the conversion of fibrinogen into monomers of fibrin, which interact and polymerize. The initially soluble polymer becomes insoluble by coagulation factors such as factor XIIIa [12]. The exudate coagulates within 3 h and forms a fibrinous material that plugs the defective area and generates attachments between adjacent tissue surfaces. The presence of blood and post-operative bleeding increases the fibrin deposition. Most of the fibrin depositions will disperse by fibrinolysis. The fibrinous mass that will remain, results in the organization and formation of adhesions [8]. Polymorphonuclear cells, macrophages, fibroblasts and mesothelial cells migrate and proliferate into the fibrinous exudate. Macrophages increase in number, change function and secrete a variety of substances that recruit mesothelial cells onto the injured surfaces. Mesothelial cells form islands, proliferate and cover the injured area. All these cells release a variety of substances such as plasminogen activator, plasminogen activator inhibitor, arachidonic acid metabolites,reactive oxygen species, cytokines, IL-1, IL-6, tumor necrosis factor-a, prostaglandin E2, collagenase, elastase and the transforming growth factors leukotriene B4 a and b(TGFa and TGFb). These factors modulate the process of peritoneal healing and adhesion formation [12-14].

http://dx.doi.org/10.5772/52694

The deposition is the key step for the healing process and the balance between deposition and degradation will determine normal peritoneal healing or adhesion formation. The fibrin absorption is controlled by fibrinolysis. The inactive plasminogen is converted to plasmin through tissue plasminogen activator (tPA) and urokinase type plasminogen activator (uPA). The tPA is present in both mesothelium and submesothelial blood vessels of serosal and peritoneal membranes[12,15]. The fibrinolytic activity normally begins three days after peritoneal injury and increases to a maximum by day 8. Therefore, those adhesions that will be formed are in place by day 8, when mesothelial regeneration has been completed [8]. Normal peritoneum has a high fibrolytic activity in order to prevent adhesion formation between different tissue surfaces. During the inflammatory process, IL-1 and IL-6 stimulate epithelial and inflammatory cells to release plasminogen activator inhibitor 1 and 2 (PAI-1 and PAI-2), which inhibit fibrinolytic activity [16]. Patients with extensive adhesions have been found to have an overexpression of PAI-1 in the peritoneum [17]. Also, the deficient blood supply, the reduced tissue oxygenation and the release of reactive oxygen species that frequently co-exist with surgical trauma, decrease the peritoneal fibrinolytic activity [9,18].

3. Adhesion prevention

In order to prevent the development and reformation of post-operative intra-abdominal adhesions a variety of surgical techniques and adjuvants have been proposed. Agents, that in theory can modify the mechanism of adhesion formation, have been evaluated in experimental trials and many of them have been advocated for use during surgery in humans. Surgical techniques are focused on the limitation of surgical trauma, prevention of ischaemia and exposure of peritoneal cavity to foreign materials (Table 1). Improvement of surgical techniques can potentially reduce adhesion formation but cannot eliminate it. Anti-adhesive agents can be classified as pharmacological agents, systemic or intra-peritoneal, and 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 [17,19].

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

Table 1. Surgical techniques for prevention of adhesion formation

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

Table 2. Pharmacological anti-adhesive agents

4. Laparoscopy and adhesions

The development of operative laparoscopy in gynaecology was associated with the expectation of reduced adhesion formation. Therefore, a large number of experimental and human clinical trials has been performed, which have shown that, compared with laparotomy, laparoscopic surgery is associated with less development of adhesions [17,20,21]. Reduction of adhesion formation is facilitated by minimal tissue handling and trauma, avoidance of exposure to foreign bodies (powder from gloves, gauze particles, e.t.c.) and prevention of air pollution in the peritoneal cavity that leads to the reduction of tissue drying. Pneumoperitoneum via increased intra-abdominal pressure has a tamponade effect that facilitates haemostasis, limits the use of diathermy and formation of ischaemic areas. In addition, laparoscopy is associated with a lower incidence of post-operative infection [21,22]. On the other hand, it has been advocated that the beneficial effect of laparoscopy in adhesion formation might be reduced by the use of pneumoperitoneum with CO2 [12]. CO2 pneumoperitoneum is associated with increased intra-abdominal pressure that compresses the splanchnic veins, reducing the blood flow by elevating vascular resistance. This stasis leads

to a reduction in tissue oxygenation, anaerobic cell metabolism, 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 [23]. Moreover it has been recently proposed that a low intra-peritoneal pressure (IPP) (8 mmHg) may be better than the standard IPP (12 mmHg) to minimize the adverse impact on the surgical peritoneal environment during a CO2 pneumoperitoneum [24].

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

Table 3. Anti-adhesive barier methods.

5. Pharmacological agents

A wide variety of pharmacological agents (Table 2) have been used in attempts to prevent or attenuate the formation of post-surgical adhesions, but none of them has been found to be effective. The use of drugs for adhesion prevention has some obstacles that affect their efficacy. Ischaemia and inadequate blood supply are important factors in adhesion formation and these also decrease systemic drug delivery inhibiting their effectiveness. Peritoneum

has an extremely rapid absorption mechanism, that limits the half life and efficacy of many intra-peritoneally administered agents. Anti-adhesion agents must not affect normal wound healing, which has steps in common with adhesion formation (fibrinous exudate, fibrin deposition, fibroblast activity and proliferation) [19,25]. The clinical effectiveness of these agents has been evaluated in a systematic review and meta-analysis that analysed data from relevant randomized controlled trials (RCT) published up to 2005 [26].

6. Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAID) affect adhesion formation by several mechanisms. They act by modifying arachidonic acid metabolism and altering cyclooxygenase activities. This results in decreased vascular permeability, platelet aggregation, and coagulation and enhanced macrophage function. A number of locally and systemically administered NSAID have been used in experimental trials.

No relevant clinical trials assessing the effectiveness of NSAID in adhesion prevention have been published to date in patients undergoing gynaecological surgery. Their clinical efficacy is questionable probably because of inadequate concentrations at the sites of surgical trauma or by rapid absorption from the peritoneal membrane [3,19,27].

7. Corticosteroids and antihistamines

Corticosteroids alter the inflammatory response by reducing vascular permeability and decreasing cytokine and chemotactic factor secretion. Antihistamines inhibit fibroblast proliferation and stabilize lysosomal membranes and histamine secretion. Corticosteroids have been used 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. In the limited data from RCT [28,29,30], no significant beneficial effect was detected with the use of corticosteroids (systemic, intra-peritoneal or Fallopian tube flushing) in the deterioration of adhesion score at second-look laparoscopy or on the probability of clinical pregnancy. However, limited data suggest that the addition of post-operative steroids to systemic intra-operative steroids might be associated with a favourable outcome both in terms of adhesion score deterioration (increase) or improvement (reduction) [31]. On the other hand, adverse events such as suppression of the pituitary–adrenal axis, immunosuppression and delayed wound healing have been reported with the use of corticosteroids [19,32,33]. Regarding 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 [31].

http://dx.doi.org/10.5772/52694

8. Progesterone and oestrogens

Progesterone has been used for the prevention of post-operative adhesions. Administration of progesterone resulted in less adhesion formation in animal models, but does not appear to be effective in humans. Oestrogens have been associated with increased adhesion formation in animal models. It was demonstrated that a hypo-oestrogenic state, produced by gonadotrophin-releasing hormone agonists or aromatase inhibitors such as tamoxifen and anastrazole, decrease development of post-operative adhesions in experimental models [3,34,35]. This hypothesis, however, has never been tested in humans.

9. Anticoagulants – Fibrinolytics

Anticoagulants such as heparin can reduce adhesion formation by inhibition of the coagulation cascade and promotion of fibrinolysis [36]. The use of heparin for intra-peritoneal irrigation in a dose that can reduce adhesion formation was associated with haemorrhage and delayed wound healing, but low-dose heparin irrigation showed no benefit in adhesion reduction [3,19,37]. In the only available RCT, heparin delivery with oxidized regenerated cellulose failed to demonstrate a superior effect compared with oxidized regenerated cellulose alone [38]. Furthermore, in experimental trials, the combination of carboxymethylcellulose or 32% dextran 70 plus heparin failed to reduce adhesion formation [38,39,40].

Fibrinolytic agents as streptokinase, elastase and tissue plasminogen activator produced by recombinant DNA techniques (rtPA) can contribute in adhesion prevention directly by reducing the fibrinous mass and indirectly by stimulating plasminogen activator activity. Systemic administration of anticoagulants is impeded by lack of safety. The concentrations of fibrinolytic agents required to prevent adhesion formation are too close to the anticoagulatory concentrations and increase the risk for post-operative haemorrhage and delayed wound healing. Intra-peritoneal administration is ineffective due to rapid absorption by the peritoneal membrane [3,25,41]. The use of carboxymethylcellulose gel and oxidized regenerated cellulose as a carrier to deliver rtPA intra-peritonealy was not associated with a reduction of adhesion formation in animal models [42,43].

A recent study has investigated the impact of gonadotropin-releasing hormone analogue (GnRH-a) on coagulation and fibrinolytic activities and its effectiveness in the prevention of pelvic adhesion after myomectomy in thirty-two infertile women. Patients treated with GnRH-a showed significant decrease in plasminogen activator inhibitorPAI, thrombin activatable fibrinolysis inhibitor (TAFI), factors V, and VIII and increased protein C (PC), but no significant change in plasminogen and α2-antiplasmin levels compared with control group, suggesting a possible critical role of the GnRH-a therapy in preventing postoperative adhesion development [44].

10. Antibiotics

Antibiotics are commonly used for prophylaxis against post-operative infections and hence 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 [45].

11. Other pharmacological regimens

Many other agents, such as apoprotin, 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 is the only one of these interventions that has been tested in the context of a RCT and 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 [29]. 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 [19,46,47].

12. Anti-adhesive barriers

The failure of pharmacological regimens to prevent adhesion formation has led to the revival of the barrier technique. With the barrier technique, traumatized peritoneal surfaces are kept separated, during mesothelial regeneration, thus 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 [19,25]. Anti-adhesive barriers are currently the most useful adjuvant for prevention of post-operative adhesion formation. Numerous substances (Table 3) have been used as mechanical barriers to separate tissue surfaces. Most of these materials are of historical interest only and had no effect or even aggravated adhesion formation [48,49]. An anti-adhesive agent should be effective, safe, economical and easy to use in both open and laparoscopic surgery [50]. The clinical effectiveness of several of these agents has been evaluated in two recent Cochrane reviews [26,51].

13. Solid barriers

Solid barriers are placed over one or between two traumatized surfaces providing a separation that averts tissue apposition during the critical period of fibrin formation and mesothelial regeneration following surgical trauma. It should be noted though, that solid barriers have some significant drawbacks. 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,

http://dx.doi.org/10.5772/52694

need suturing and are difficult to use via laparoscopic surgery. Their benefits are also limited to the site of application and do not prevent the development of adhesions at sites of indirect trauma. So the surgeon has to surmise where adhesions will be formed in order to choose the placement sites and optimize barrier efficacy [52]. Not infrequently, this proves to be a challenging task, since, for example, midline laparotomy initiates a generalized peritoneal response that can lead to adhesion formation distant from surgical trauma [53].

14. Expanded polytetrafluoroethylene

Expanded polytetrafluoroethylene (Preclude, Gore-Tex Surgical Membrane; Johnson and Johnson, Arlington, TX) 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 [54]. Moreover, when compared with oxidized regenerated cellulose, Preclude was found to be more effective in terms of adhesion reformation after adhesiolysis [55]. However, 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 to oxidized regenerated cellulose [56]. Expanded polytetrafluoroethylene has the disadvantages that it must be sutured in place, is difficult to use in laparoscopic surgery and, ideally, requires a subsequent surgical procedure for removal after the injury has healed [57]. 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 [25].

15. Oxidized regenerated cellulose

Oxidized regenerated cellulose (Interceed (TC7); Johnson and Johnson) is the first degradable barrier that was used in clinical practice and represents a modification of its precursor Surgicel, which has been used as a haemostatic agent for a long time. It is a 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 [3,22]. Oxidized regenerated cellulose use in laparoscopic surgery is feasible [8]. In order to evaluate the efficacy of oxidized regenerated cellulose in the prevention of the development of post-surgical adhesions, many studies have been carried out. A meta-analysis of 11 relevant RCT [51] 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 [58-62]. In laparotomy, the available RCT [63-68], when meta-analysed [51], demonstrated that a significant reduction in the reformation (or mixture) of adhesions can be expected with the use of oxidized regenerated cellulose as compared with the no treatment group. The product is site specific, thus 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 [8,69,70]. In addition, as reported previously, the 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 [36,38,40]. Oxidized regenerated cellulose has been approved by the US Food and Drink Administration (FDA) for use in open surgery in the USA [69].

16. Hyaluronic acid

Hyaluronic acid (HA) is a linear polysaccharide with repeating disaccharide units that are composed of sodium D-glucuronate and N-acetyl-D-glucosamine. It is a naturally occurring component of many body tissues and fluids, where it provides mechanically protective and physically supportive roles [69]. Various combinations of HA have been used for the prevention of adhesion formation. HA and carboxymethylcellulose (Seprafilm; Genzyme, Cambridge, Massachusetts, USA) is an absorbable membrane that dissolves and forms a hydrophilic gel approximately 24 h after placement. It is a site-specific barrier and acts by separating mechanically opposite tissue surfaces and lasts for 7 days. The HA is completely cleared from the body within 4 weeks, but the 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 [71,72]. Its use in laparoscopic procedures is difficult. 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 [72]. Potential side effects include induced foreign body reaction, higher incidence of pulmonary emboli and intra-peritoneal abscess formation, but these findings were not statistically significant in the relevant trials [3,73]. High cost is another limitation because, for an effective protection from intestinal obstruction, a mean of 4.5 sheets per patient is required [25]. Seprafilm has been approved by the FDA for use in open surgery in the USA [22]. Ferric hyaluronate 0.5% gel (Intergel; Gynecare, Sommerville, New Jersey, USA) is a viscous gel that provides a broader coverage than previous site-specific agents. It was shown to be easy to use in open and laparoscopic surgery. In relevant prospective randomized trials, ferric hyaluronate was associated with a significant reduction of severity and extent of post-operative adhesions and statistically significant improvement of the American Fertility Society (AFS) and modified AFS scores at second-look laparoscopy [69,74,75]. It was withdrawn from the market in 2003 because of problems with late onset post-operative pain and rare reports of sclerosing peritonitis [25,76]. Low-viscosity 0.04% HA combined with phosphate-buffered saline (Sepracoat; Genzyme) is a bioabsorbable macromolecular dilute solution of HA that is cleared from the body in less than 5 days. The solution is applied in the peritoneal cavity before any tissue manipulation in order to protect peritoneal surfaces

http://dx.doi.org/10.5772/52694

from indirect trauma and finally before the end of the procedures [3,77,78]. In a blind, prospective, randomized, placebo-controlled multicentre study, where patients had undergone open gynecological procedures, low-viscosity 0.04% HA resulted in a statistically significant reduction of adhesions, as well as of the mean adhesion score, at second-look laparoscopy. However, it was not effective in reducing post-operative adhesion formation at sites of direct surgical trauma [78]. It has been approved by the FDA for use in open surgery in the USA [22]. HA cross-linked to HA (Hyalobarrier Gel; Baxter, Bracknell, UK) is a site-specific highly viscous gel is considered as easy to use in laparoscopic and open surgery. In a prospective, randomized, controlled study where the rate of post-surgical adhesions after laparoscopic myomectomy was examined, cross-linked HA resulted in significantly more adhesion-free patients [79]. Pregnancy rates at 6 and 12 months after laparoscopic myomectomy were significantly higher in patients treated with cross-linked HA [80]. 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 [81]. 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. Auto-cross-linked internal ester form of HA (ACP gel; Fidia Advanced Biopolymers, AbanoTerme, Italy) has the biocompatibility of the original polymer but higher viscosity and extended residence. It is a gel that has been shown to be efficacious in reducing abdominal adhesions in experimental models [82,83]. 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 [84,85]. 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. Cross-linked thiol-modified HA with 4% polyethyleneglycoldiacrylate (Carbylan-S and Carbylan-SX; CarbylanBioSurgery, Palo Alto, CA, USA) is 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 [52,86].

17. Polylactide

Polylactide (copolymer of 70:30 poly(L-lactide-CO-D, L-lactide; SurgiWrap, MacroporeBiosurgeryinc., San Diego, USA) is a 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, polylactide appears to be effective in the reduction of adhesion formation, but there are no data currently for safety and efficacy in humans [87,88].

18. Polyethylene glycol

Polyethylene glycol (SprayGel; Confluent Surgical, Waltham, Massachusetts, USA). It is a 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 [89]. Drawbacks of the product are the intricacy of preparation and application, the time required to cover the target tissue and the high cost. In a prospective randomized controlled phase-III trial, in 40 patients undergoing myomectomy, polylactide 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. Also, the proportion of adhesion-free patients at second-look laparoscopy was increased in the treatment group but the difference was not statistically significant [89]. It has been approved for use in laparoscopic and open surgery in Europe, but by the FDA only for use in open surgery in USA [22,25].

19. Carboxymethylcellulose

Carboxymethylcellulose is a 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. A composite gel of carboxymethylcellulose and polyethylene oxide (Oxiplex; FzioMed, San Luis Obispo, CA, USA) is a viscoelastic gel, which acts as a barrier between tissues that inhibits protein deposition and thrombus formation [74]. The gel is absorbed by 6 weeks, but 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 [90]. 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 [74,91]. Another double-blind prospective randomized controlled trial has shown that the mean AFS score for patients in the treatment group was unchanged, while in control patients an increased AFS score was noted [91]. 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 [25].

20. Fibrin glue

Fibrin glue (Tissucol; Baxter International, Deerfield, IL, USA) is a biological product. Fibrin glue is made by mixing human fibrinogen with bovine thrombin, calcium and factor XIII

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[92]. Obviously, the use of human blood products raises a theoretical risk for transmission of infectious diseases. According to the pathogenesis of adhesions, application of fibrin glue at the traumatized peritoneal surfaces should increase adhesion formation. Possibly, fibrin glue application confines fibrin deposition and averts the development of attachments between opposing tissue surfaces. In animal studies, the use of fibrin glue has been shown to decrease adhesion formation and reformation but clinical data are limited. Fibrin glue has not been approved by the FDA for use in USA [22,47]. So far, no relevant data from trials in humans have been published.

21. Carboxymethylchitosan

N,O-carboxymethylchitosan (Adhes-X, Chitogenics, New Jersey, USA) is a purified derivative of chitin obtained from the exoskeleton of shrimp and has similar structure to hyaluronic acid and carboxymethylcellulose [93]. 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, demonstrated a 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 [94].

22. Fluid barriers

Fluids constitute an ideal barrier agent because their action is not limited to the site of application. Their function is provided by hydrofloration of intra-peritoneal structures in the liquid that is infused into the peritoneal cavity at the end of the surgical procedure. Hydrofloration provides a temporary separation between raw peritoneal surfaces allowing independent healing without the formation of adhesions. Possibly, fluid circulation in the peritoneal cavity contributes to the prevention of adhesion formation by diluting fibrinous exudates released from traumatized surfaces. Fluid barriers may prevent adhesion formation both at the traumatized area and elsewhere in the pelvis. The instillation of fluids in the peritoneal cavity may be associated with some undesirable side effects, such as leakage from the incision, labial oedema, feeling of fluid moving around, abdominal discomfort, abdominal distension and complications such as pulmonary and peripheral oedema. Large volumes of intra-peritoneal fluids may decrease the peritoneum ability to confront bacterial infections [3,17,76].

23. Crystalloid solutions

Crystalloid solutions (Ringer's lactate, NaCl 0.9%) are rapidly absorbed by the peritoneal cavity, at a rate of 30–50 ml/h. Consequently, 24 h after the surgery, minimal or no crystal-

loid solution would be left in the peritoneal cavity. The instillation of crystalloids does not seem to result in decreased adhesion formation. They are commonly used but they are not approved for use as anti-adhesive agents [25,69,95]. Crystalloids have also been used in various combinations with heparin, steroids, antihistamines and other pharmacological agents in randomized controlled trials, but none of them has been found effective in decreasing post-operative adhesion formation or improving pregnancy rates [96].

24. Dextran

Dextran (32% dextran 70; Hyskon; Pharmacia, Piscataway, New Jersey, USA) is a 1–6-linked dextrose polymer. A summary [26] of the available data from relevant RCT [37,97-99] demonstrated a decreased proportion of patients with 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. In addition, its use was associated with significant side effects as pulmonary and peripheral oedema caused by its osmotic properties, liver function abnormalities, pleural effusion and, rarely, allergic reactions or anaphylactic shock and disseminated intra-vascular coagulation. It has not been approved for use as an anti-adhesive agent [3,17,100,101].

25. Polyglycan esters

Polyglycanesters (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 [102].

26. 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 [103]. 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 [104]. 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 adhesion lysed at initial surgery had the greater reduction in adhesion incidence [95]. A stratified analysis of these two studies revealed a statistically significant effect oficodextrin 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 [105]. 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 [76,106]. Low cost is another advantage of icodextrin 4%. Adept (1.5 litre bags) are about half the price of each sheet of Interceed or Seprafilm and it is about four times cheaper than one SprayGel package [50]. 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 [25,76,91,95].

27. Conclusions

Development of post-operative adhesion is a widespread consequence of surgical trauma and healing following open or laparoscopic gynecological surgery and is associated with significant complications. At present, the main strategy to avoid formation and reformation of adhesions is focused on the use of careful surgical techniques and anti-adhesive agents. Reduction of adhesion formation after laparoscopic surgery in comparison to the more conventional approach by laparotomy can be attributed to less tissue manipulation, less tissue drying, avoidance of insertion of foreign bodies such as talc from the surgical gloves, fibers from the gauzes e.t.c. On the other hand pneumoperitoneum during laparoscopy exerts a tamponade effect that facilitates hemostasis, so minimizing the use of electrocautery, which is known that leads to the formation of ischaemic areas and therefore predisposing to adhesion formation. The use of CO2 for pnemoperitoneum may lead to adhesion formation, since its use is associated with reduction in tissue oxygenation, acidosis and release ofreactive oxygen species, which are considered adhesiogenic. Therefore, the addition of oxygen, the heating of the insufflatedCO2 or the alternative use of other gases (i.e. helium) may be beneficial in terms of reduction of *de novo* adhesion formation. At the end of each operation an «underwater» examination should be used in order to document complete intra-peritoneal hemostasis, since it has been clearly demonstrated that incomplete hemostasis is associated with adhesion formation.

Finally, several anti-adhesive agents are used during laparoscopic intrventions, in order to minimizepostoperative adhesions. These fall into two main categories, which include pharmacological agents and barrier methods. Limited data support the use of the former, either locally or systemically. Barriers, which mechanically separate the opposed serosal surfaces and exert their beneficial action, at least partly, because they remain in place beyond the critical 3-day point, at which competition of fibrinolytic activityandfibrosis will lead to adhesion formation. The tissue separation can be achieved either by the use of solid (films or gel) or fluid barriers. The clinical effectiveness of several of these agents has been thoroughly evaluated in two recent Cochrane reviews by Metwally et al [26] and Ahmad et al [51].

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