Peritoneal Adhesions and their Prevention - Current Trends

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ABSTRACT

The development of adhesions after gynecologic surgery is a severe problem with ramifications that go beyond the medical complications patients suffer (which most often include pain, obstruction and infertility), since they also impose a huge financial burden on the health care system and increase the workload of surgeons and all personnel involved in surgical follow-up care. Surgical techniques to avoid adhesion formation have not proven to be sufficient and pharmaceutical approaches for their prevention are even less effective, which means that the use of adhesion prevention devices is essential for achieving decent prophylaxis. This review explores the wide range of adhesion prevention products currently available on the market. Particular emphasis is put on prospective randomized controlled clinical trials that include second-look interventions, as these offer the most solid evidence of efficacy. We focused on adhesion scores, which are the most common way to quantify adhesion formation. This enables a direct comparison of the efficacies of different devices. While the greatest amount of data are available for oxidized regenerated cellulose, the outcomes with this adhesion barrier are mediocre and several studies have shown little efficacy. The best results have been achieved using adhesion barriers based on either modified starch, i.e., 4DryField® PH (PlantTec Medical GmbH, Lüneburg, Germany), or expanded polytetrafluoroethylene, i.e., GoreTex (W.L. Gore & Associates, Inc., Medical Products Division, Flagstaff, AZ), albeit the latter, as a non-resorbable barrier, has a huge disadvantage of having to be surgically removed again. Therefore, 4DryField® PH currently appears to be a promising approach and further studies are recommended.

BACKGROUND

Peritoneal healing and adhesion formation

Following surgical trauma, the time required for regeneration of the peritoneum and its mesothelial layer is 5-6 days.[1-3] The cellular sequence of this repair starts with polymorphonuclear leukocytes (PMN) attaching to fibrin strands, followed by infiltration of macrophages, which form a single-cell layer to cover the wound surface by day 2. During the following days, primitive mesenchymal cells and first mesothelial cells, followed by proliferating fibroblasts, can be observed until a single layer of mesothelial cells, interconnected by desmosomes and tight junctions, is present on the wound surface on day 5. By then, PMNs have vanished and the amount of fibrin has decreased significantly. The amount of macrophages also begins to decrease from day 5 onwards; a continuous basement membrane forms beneath the mesothelial coverage and blood vessels begin to develop.[4,5] The most probable origin of the new mesothelial cells is mesenchymal stem cells within the connective tissue.[6] The mesothelial cells are attracted to the injury site chemotactically, where they initially form islands and then proliferate to complete the re-epithelialization.[5,7] Healing of the visceral peritoneum does not seem to differ significantly from that of the parietal peritoneum, apart from different time intervals of some healing stages.[5,8,9]

The pathophysiology of adhesiogenesis after surgical injury generally depends on exudation,[10] inflammation and fibrin deposition. Inflammatory responses are triggered by ischemia in the damaged tissue through the release of inflammatory mediators from mesothelial cells, as well as pro-coagulatory and anti-fibrinolytic reactions.[11] An imbalance between fibrinolytic and pro-coagulatory factors leads to the persistence of the formed polyfibrin, which under normal physiological conditions would be degraded by the fibrinolytic activity of the mesothelium.[12-14] The fibrinolytic system is activated through tPA (tissue-type plasminogen activator), which cleaves plasminogen to yield active plasmin. The protease plasmin then cleaves fibrin and, therefore, can dissolve polyfibrin strands.[12] However, reduced tPA activity has been found in peritoneal tissue as a local response to surgical trauma, causing (at least in part) a decline in fibrinolytic capacity.[13] Inhibition of tPA can be triggered by plasminogen-activator-inhibitor (PAI). Inflammatory reactions lead to an increased release of PAI and, thus, can also lead to an inhibition of the fibrinolytic system.[15] Once fibrin bridges have formed between neighboring tissues or organs that are not normally connected to one another, these mature into adhesions.[16] A multitude of growth factors, cytokines and signaling molecules are involved in this process.[16,17] The maturation of adhesions includes vascularization, which is highly dependent on VEGF expression.[17] As in fibrosis, connective tissue formation is mediated by connective tissue growth factors, as well as TGF-betas.[18,19]

The main intra-operative factor promoting adhesion formation is injury to the peritoneum.[20,21] Other factors include the complexity of the procedure,[22] tissue necrosis through heavy coagulation [23] and bacterial inflammation.[24] For laparoscopic procedures, desiccation through dry insufflation gas, as well as high insufflation pressure (also leading to the compression of capillary flow) [25-27] and mesothelial hypoxia through CO_2 [28] have to be considered as possible contributors to adhesion formation. For laparotomies, these possible contributors include desiccation as a result of heat and/or light [23] and mesothelial desiccation/abrasion from dry swabs.[20,21]

Foreign bodies can also provoke adhesions; possible sources include suture materials,[2,10,29] surgical glove dusting powders,[30] material extruded from the digestive tract, and hernia meshes.[24,29,31,32]. The likelihood of adhesion formation is also influenced by the procedure performed, and ovarian cystectomy, endometriosis, myomectomy, adhesiolysis, tubal surgery including ectopic pregnancies, and surgical treatment of pelvic inflammatory disease are associated with relatively high adhesiogenicity.[33]

THE AFTERMATH

Medical complications

Adhesions are the main cause of chronic abdominal pain,[34] small bowel obstructions,[34-36] and secondary female infertility.[34-36] Chronic abdominal pain can be divided into continuous and colicky pain. While adhesions more often cause the latter, they can also cause continuous pain when they retract the viscera without obstructing them.[37] The actual effect of adhesions on pain is difficult to estimate since the pathophysiology of chronic abdominal pain is still poorly understood.[38] Seventy-four to 86% of all cases of small bowel obstruction can be ascribed to post-surgical adhesions,[39,40] which are also the only factor causing female infertility in 15% of cases.[41] Infertility can be caused by either peri-tubal adhesions affecting tubal motility and ovum transport or adhesions around the ovaries inhibiting follicular growth.[24] Although adhesiolysis surgery may increase the fertility of previously infertile women, the surgery itself imposes a risk of (re-)formation of adhesion and, thereby, persistence or even aggravation of the problems caused by the adhesions. Adhesions or adhesion-related complications are also some of the main reasons for readmission. It was found that 33% to 44% of patients with extensive open surgery were readmitted either directly or likely due to adhesion-related complications within 10 years.[35,42,43] With 48% and 41% of women being readmitted, respectively, surgical procedures on the ovary and fallopian tube have been shown to have the highest risk of adhesion-related readmission.[35] Furthermore, adhesions are one of the main reasons for conversion during subsequent surgeries.[44,45] Adhesiolysis prolongs surgery and post-surgical recovery and increases the risk of intra-operative accidental damage of neighboring tissues and organs and post-surgical complications.[46-48] A meta-analysis found that the overall incidence of adhesiolysis-related enterotomy in gynecologic surgeries was 4.8% (95%CI: 0.6-9.1%).[49] Another meta study found that the incidence rate correlates with the number of previous laparotomies and the presence of bowel fistula.[50] While the incidence rate of ureteral injuries was considerably lower, and regularly below 1%, adhesions were considered to be a predisposing factor.[51,52]

Economic impact

While the possible medical impact of adhesions is well known among surgeons, the extent of the economic ramifications of adhesions is often neglected. Several studies have examined the economic impact of adhesions and adhesion-related complications. The costs associated with hospital stays due to adhesive small bowel obstructions were examined by

Menzies et al.[53] In an analysis of over 100 cases, they found that the costs for referral, follow-up, hospital ward/ICU stay, theater time, investigations and drugs added up to over 4,600 GBP per patient when surgical treatment was necessary (37% of cases), while conservative treatment still required a total cost of over 1,600 GBP per patient. A prospective study by Ivarsson et al.[54] to assess the direct costs of bowel obstruction resulting from adhesions found that 60% of bowel obstructions were caused by adhesions, and 60% of patients who required operative treatment experienced major complications including death. The authors extrapolated the expenses to the national level of Sweden, and estimated that adhesive small bowel obstructions lead to over 2,300 hospital admissions annually, which is equivalent to 26 per 100,000 people, and total costs of about $13 million. Ray et al.[55] examined inpatient care and expenditures related to abdominal adhesiolysis in the United States in 1994. They found that adhesiolysis was responsible for over 300,000 or 1% of hospitalizations, which is equivalent to 117 adhesion-related hospitalizations per 100,000 people. This sums up to almost 850,000 days of inpatient care and direct costs of about $1.3 billion for hospitalization and surgeon expenditures. The addition of adhesiolysis to other surgical procedures added ≈1-2 days of inpatient care. A population-based study by Kössi et al.[56] of the surgical workload and economic impact of bowel obstruction caused by postoperative adhesions found that 29% of hospitalized patients needed surgery with a mean hospital stay of 11-19 days, for a total of 1,118 inpatient days. Extrapolation to the national level of Finland yielded total costs of inpatient episodes of over 2 million £ and an extra 124 days in the operating theater. Tingstedt et al.[57] conducted a long-term follow-up and cost analysis following surgery for small bowel obstruction caused by intra-abdominal adhesions for 102 patients with surgery for adhesion-caused small bowel obstruction. During the follow-up period (median = 14 years), 102 patients experienced 273 episodes (2.7 per patient) of intestinal obstruction (after the index operation). Of these, 87% resulted in inpatient readmission and 47% resulted in further surgery. The cost of adhesion-related problems in this study was almost 1.6 million €, which is equivalent to 6,702 € per inpatient episode. With annual costs in Sweden between 40 and 60 million €, the costs of inpatient readmission are almost as high as those for gastric cancer. The inpatient burden of abdominal and gynecological adhesiolysis in the United States was analyzed by Sikirica et al.[58] They found that, in 2005, there were over 350,000 adhesiolysis-related hospitalizations, of which 23% were for primary and 77% were for secondary adhesiolysis. Almost 1 million days of care were attributed to adhesiolysis-related procedures and inpatient expenditures totaled $2.3 billion ($1.4 billion for primary and $926 million for secondary adhesiolysis). Of the secondary adhesiolysis procedures, 46% involved the female reproductive tract, for a total of 57,000 additional days of care and attributable costs of $220 million. In summary, multiple factors contribute to the financial burden of adhesions, including additional surgeries, further and longer hospitalizations, supplementary investigations and drugs, prolonged and more severe re-interventions, as well as longer recovery times and more frequent follow-up care visits. An additional factor that is often overlooked is the loss of productivity: surgeons, hospital personal and aftercare physicians have to invest time in the treatment of adhesion-related complications, and hospital beds and operating rooms are unnecessarily occupied. Considering the huge economic impact of adhesions and adhesion-related consequences, the routine use of effective adhesion prevention measures would appear to be mandatory. Wilson [59] developed an economic model to assess how effective adhesion barriers needed to be if they were to be economically viable due to a reduction in readmissions based on the Surgical and Clinical Adhesions Research Group (SCAR) database. It calculates the percentage reduction in readmissions (efficacy) that an adhesion-reduction product must achieve to return the cost of investment. For this purpose, he compared the cumulative costs of adhesion-related readmissions since surgery per patient without treatment (control) and with an adhesion barrier priced at 130 € per treatment. The model was designed to yield the required efficacy to return the cost of treatment after 1 or 3 years. For 1 year, amortization of the costs requires an efficacy of 53%, and for 3 years, this falls to 26%. The author concluded that the use of an anti-adhesion product with a cost of 130 € and an efficacy of 25% for one year in the UK could save over 40 million € over the following 10 years.

ADHESION PREVENTION WITHOUT BARRIERS

Adapted surgical techniques

The most obvious and effective strategy for adhesion prevention is to avoid surgery.[60] If this is not an option, surgical techniques that minimize trauma and post-operative contact of injured sites should be chosen.[60] For this purpose, careful tissue handling and minimization of electrocoagulation should be implemented and manipulation of the peritoneum should be avoided as much as possible. Furthermore, the level of desiccation and abrasion and the subsequent damage to peritoneal cells can be minimized through frequent moistening of the surgical area as well as of the gas used, the avoidance of dry swabs and towels and the reduction of heat and light. Care should be taken to avoid chronic inflammatory reactions that may be caused by foreign bodies and favor adhesion formation.[61] Since laparoscopic approaches produce less peritoneal trauma than open surgery, adhesion formation can indeed be reduced, but not prevented.[62] Even laparoscopy introduces new problems like hypoxia of peritoneal cells, which can be induced by increased intra-abdominal pressure compressing supporting blood vessels [28] or through laparoscopic graspers that apply far more pressure on tissues than what is actually be needed to hold them, thereby causing significant tissue damage.[63,64] An epidemiological study found that the overall risk of adhesion-related readmission following laparoscopic and open surgeries is comparable.[65] Although instillation of crystalloid solutions is a widespread approach to reduce adhesion formation, a meta-analysis of clinical studies using Ringer's lactate (RL) or saline solution conclusively showed no reduction in adhesion formation.[66] As polyfibrin strands are the basic building blocks during adhesion formation and blood is the primary source of fibrin,[67,68] effective hemostatic measures are the foundation of adhesion reduction.[69]

Pharmaceutical approaches

Pharmaceutical approaches for adhesion prevention target the underlying mechanisms of adhesion formation. Steroids have been used due their anti-

inflammatory effects,[70,71] heparin because of its anti-coagulatory effect,[72-74] tissue-plasminogen activator (t-PA) because it catalyzes plasmin activation, which in turn cleaves fibrin,[75] and promethazine because it is an antagonist of the inflammation-mediating histamine in combination with the steroid dexamethasone.[76] Despite this reasoned approach, no success has been achieved with the use of pharmaceuticals for adhesion reduction.[77] A possible explanation for this poor result might be their rapid clearance from the serosal cavity.[78,79] Additionally, it has been suggested that the use of only one extracellular mediator might be insufficient to have an outcome, while the combination of several might show a synergetic effect.[80,81] Although slight progress has been made with the additional use of drug-releasing barrier systems in an animal model,[82] no comprehensive data are available. For pharmaceutical approaches, their permanency and side effects during the healing process are an additional issue to be considered.[83] For example, corticosteroids are associated with immunosuppression and poor wound healing, the latter of which is also a problem with the use of anti-fibrinolytics.[33]

In conclusion, adapted surgical techniques and pharmaceutical approaches alone are not able to sufficiently prevent adhesion formation. Therefore, additional measures are required, which is where adhesion barriers come into play.

Adhesion barriers

A multitude of barriers are available for adhesion prevention. These can be categorized based on the state of matter (liquid, semi-solid, solid), which is in a certain form (gauze, membrane, sheet, powder, gel and so forth). Efficacy, retention time and side effects primarily depend on the material used, rather than on the form in which it is delivered. Considering the disadvantages of these possible classifications, in this review, adhesion barriers are sorted by material, taking into account an adequate degree of detail, as well as efficacy, retention time and side effects. Most barriers are based on organic polymers, with polysaccharides being the most common superordinate category.

Strong emphasis is placed on prospective, randomized controlled clinical trials with second-look intervention. These enable the best possible evidence of efficacy based on the direct assessment of adhesion formation, most commonly using adhesion scores for quantification. Alternatively, results are expressed as rates of adhesion-free outcome and adhesion incidence. These approaches do not consider the impact of the barriers on adhesion reduction when adhesions form nonetheless. Adhesion score results also consider adhesion-free outcomes (with a value of zero), and thus provide the highest explanatory power. Accordingly, these are the outcomes focused on in the present review and given whenever possible. Additionally, as the title suggests, this review deals with peritoneal adhesion formation. Therefore, RCTs dealing with other approaches (e.g., intrauterine adhesion prevention) are discussed only briefly.

Table I provides an overview of the gynecologic RCTs that have examined adhesion-barrier efficacy using either saline solution, RL or no adhesion prevention treatment for the control. Adhesion scores are presented whenever available.

Icodextrin

Aqueous solutions of icodextrin were originally used for peritoneal dialysis. The colloid osmotic agent icodextrin increases the osmotic pressure, initiating transudation of serum, which compensates for absorption of fluid into the lymphatic system to prolong the prevalence.[77,84] For adhesion prevention, the effect is based on the principle of hydroflotation. After application, the organs float in the solution, thereby preventing their direct contact, which is necessary for the formation of adhesions.[85] In addition to this effect, factors mediating adhesion formation are diluted. The only icodextrin preparation that is currently available for adhesion prevention is Adept® from Baxter (Deerfield, IL, USA), which, according to the product's instructions for use, is only indicated for gynecologic laparoscopic adhesiolysis surgery. There are two published second-look RCTs on the use of Adept® for adhesion prevention in gynecology. Both used RL for the control group. Brown et al.[86] included 402 women undergoing laparoscopic gynecological adhesiolysis. Although AFS scores were apparently used, the net scores were not given. The main result is expressed as "clinical success", which is defined as "the percentage of patients in whom the number of sites with adhesions decreased by at least three or 30% of the number of sites lyzed". This success rate in the Adept® group (49%) was significantly greater than that in the control group (38%). The ratio of patients with significantly reduced pelvic pain was the same in both groups.

Trew et al.[87] examined the outcomes with Adept® in 330 women undergoing laparoscopic removal of myomas or endometriotic cysts. The mean total mAFS score was 8.4 in the control and 8.1 in the Adept® group (not statistically significant) and the mean number of de novo adhesions was 2.6 in both groups. The authors stated that there was no evidence of a clinical effect.

Additionally, several studies on the use of Adept® in animal models showed no significant adhesion reduction[88-91] and, in an animal peritonitis model, Adept® even increased adhesion formation, as well as abscess formation.[92]

Further drawbacks of Adept® arise from its incompatibility with the placement of drainages.[60] Furthermore, Adept® is contraindicated in the presence of frank infections (e.g., peritonitis) in the abdomino-pelvic cavity, in procedures with laparotomy incisions (where it could lead to serious post-operative wound complications), and in procedures involving bowel resection or repair or appendectomy (where anastomotic failure, ileus and peritonitis could occur), according to the product's instructions for use.

Expanded polytetrafluorethylene (ePTFE)

In contrast to most other materials that are used as a basis for adhesion barriers, PTFE is synthetic. It is a hydrophobic polymer that is commonly known under the brand name Teflon™. For medical applications, expanded PTFE grafts are made by extrusion of PTFE resin mixed with a lubricant. Manufactured into thin sheets of 0.1 mm gauge, it is used as a non-resorbable adhesion barrier under the trade name Gore-Tex Surgical Membrane® (W.L. Gore & Associates, Inc., Medical Products Division, Flagstaff, AZ, USA). Unlike other solid barriers, it has to be fixed by suture.[93]

The efficacy of the Gore-Tex Surgical Membrane® was examined after myomectomies in 27 patients.[94] Only patients with two separate incisions were included; one was treated with the ePTFE membrane while the other was left untreated. Using an adhesion score

Table I
Overview of randomized controlled trials on the prevention of peritoneal adhesion in gynecology with second-looks and a control group receiving saline solution, Ringer's lactate (RL) solution or no treatment

Material	Product name	Indication	No. of patients[a]	Main outcome[b]	Outcome Control	Outcome Intervention	Improvement[c]	Significant	Ref.
Icodextrin	Adept®	Removal of myomas or endometriotic cysts	330	Score (mAFS)	8.4	8.1	4%	No	87
Icodextrin	Adept®	Adhesiolysis	402	"Clinical success"	38%	49%	11%	Yes	86
ePTFE	Gore-Tex Surgical membrane	Myomectomy	27	Score	7.6	1.0	87%	Yes	94
ORC	Interceed®	Endometriosis resection	32	Adhesion- free patients	75%	13%	62%	Yes	100
ORC	Interceed®	Myomectomy	50	Adhesion- free patients	60%	12%	48%	Yes	101
ORC	Interceed®	Ovarian cystectomy	17d	Adhesion- free outcome	76%	35%	39%	Yes	102
ORC	Not specified	Intracapsular myomectomy	694	Rate of adhesions	23% (laparoscopy) 28% (laparotomy)	16% (laparoscopy) 22% (laparotomy)	7% (laparoscopy) 22% (laparotomy)	No	62
ORC	Interceed®	Endometriosis resection	40	Score	1.1	0.4	64%	No	103
ORC	Interceed®	Polycystic ovarian syndrome	21[d]	Adhesion incidence	33%	43%	-10%	No	106
ORC	Interceed®	Polycystic ovarian syndrome	8[d]	Score	6.7	9.9	-48%	No	107
ORC	Interceed®	Adhesiolysis (with hydrocortisone instillation)	28[d]	Score	0.9	0.7	22%	No	104
ORC	Interceed®	Adhesiolysis on ovaries, fallopian tubes, and fimbriae	66[d]	Severity score	4.9	6.8	-39%	Yes	108
ORC	Interceed®	Adhesiolysis	63[d]	Adhesion incidence	76%	41%	35%	Yes	97
ORC	Interceed®	Endometriosis resection	28[d]	Adhesion incidence	82%	50%	32%	Yes	97
ORC	Interceed®	Ovarian diseases	55[d]	Severity score	1.1	0.8	27%	No	105
HA	HyaRegen®	Removal of adhesions, myomas, ovarian cysts or endometriotic cysts	215	Score (mAFS)	0.9	0.3	67%	Yes	125
HA	Hyalobarrier	Myomectomy	52	Score	2.1	2.1	0%	No	126
HA	Intergel®	Peritoneal cavity surgery	23	Score (AFS)	Not specified	Not specified	Not specified	Yes	122
HA	Intergel®	Peritoneal cavity surgery	147	Score (mAFS)	1.3	0.5	54%	Yes	123
HA	Intergel®	Peritoneal cavity surgery	265	Score (mAFS)	2.3	1.3	43%	Yes	124
HA/CMC	Sepraspray®	Myomectomy	41	Change of score (mAFS)	1.6	0.7	53%	No	138
HA/CMC	Seprafilm®	Myomectomy	127	Score	2.4 (severity) 1.7 (extent)	1.9 (severity) 1.2 (extent)	21% (severity) 1.2 (extent)	Yes	140
Modified starch	4DryField®	Endometriosis resection	manuscript in preparation	Score	manuscript in preparation	manuscript in preparation	manuscript in preparation	manuscript in preparation	146
PEG	SprayGel™	Myomectomy	66	Severity score	1.9	1.0	47%	Yes	154
PEG	SprayGel™	Myomectomy	58	Score (mAFS)	2.6	1.1	58%	Yes	155
PEG	SprayGel™	Adhesiolysis, salpingotomy and/or cystectomy	15	Score	2.4	1.2	50%	No	156
PEG	SprayShield™	Myomectomy	15	Score	1.6 (severity) 0.9 (extent)	0.8 (severity) 0.6 (extent)	50% (severity) 33% (extent)	No	157
PEG	OxiPlex/AP Gel or Intercoat	Adnexal surgeries	49	Score (AFS)	15.8	9.1	42%	Yes	158
PEG	Oxiplex/AP Gel or Intercoat	Resection of endometriosis	37	Score (AFS)	14.0	6.2	56%	Yes	159
PEG	Oxiplex/AP Gel or Intercoat	Adnexal surgery	28	Score (AFS)	11.6	8.1	30%	No	153

a: number of patients in the primary outcome evaluation; **b:** if an adhesion score was given, this was always used as the main outcome; **c:** calculated as (Control-Intervention)/Control*100 for outcomes not measured in %,u and by direct subtraction for outcomes measured in %; bold values are adhesion score results; **d:** study used intra-patient controls (one side treated with the respective product and the other side served as an untreated control); thus, all patients belong to both groups. mAFS, modified American Fertility Society; ePTFE, expanded polytetrafluorethylene ; ORC, oxidized regenerated cellulose; HA, hyaluronic acid; HA/CMC, hyaluronate + carboxymethylcellulose; PEG, polyethylene glycol

ranging from 0 to 11, a statistically significant reduction from 7.6 to 1.0 could be achieved. Haney et al. compared the impact of ePTFE (Gore-Tex Surgical Membrane®) and oxidized regenerated cellulose (ORC) (Interceed®; Ethicon, Inc., Somerville, NJ, USA) after gynecologic adhesiolysis.[95] They used both products in 32 patients covering the left and right pelvic sidewalls, respectively. The same scoring system as in the aforementioned study was used. While ePTFE again gave a score of 1.0, ORC gave a significantly higher score of 4.8.

PTFE is among the most inert biomaterials known, resisting biologic degradation even after several years in vivo. However, the long-term implications of leaving PTFE in the abdominal cavity remain unknown.[94] The need for removal considerably limits its usage [96] and could promote further adhesion formation after the required re-intervention for product removal. Therefore, the positive anti-adhesive effect of ePTFE is limited to the time between the initial surgery and the re-intervention for product removal.

Oxidized regenerated cellulose (ORC)

Regenerated cellulose is manufactured from natural cellulose sources like wood in a process that basically modifies and rearranges its structure. Controlled oxidation of the product leads to ORC, which can be manufactured into fabrics for medical applications. The most commonly known and used preparation of ORC is Interceed®, an absorbable off-white knitted fabric from Ethicon (Somerville, NJ, USA). Interceed® adheres to deperitonealized areas without suturing and forms a soft, gelatinous mass, which protects the tissue during re-epithelialization.[97] According to its instructions for use, Interceed® is absorbed over 4 weeks. Apart from acting as a physical barrier to isolate wound sites, additional effects have been ascribed to ORC. For example, in cell culture experiments, it increased the tissue plasminogen activator (tPA)/plasminogen activator inhibitor (PAI) 1 ratio in fibroblasts isolated from adhesion tissues.[98] Furthermore, it reduced the secretion of inflammatory mediators by acting on macrophages' ability to interact with scavenger receptor ligands, another potential mechanism to decrease adhesion formation.[99]

ORC is the adhesion barrier for which the highest number of RCTs (n=12) concerning gynecologic applications have been published. However, only four of them reported statistically significant efficacy in comparison to untreated controls; of the remaining eight, six did not find any significant differences between ORC and untreated controls and two even found that the control was significantly superior (one of them was versus an active control). Two of the four trials describing significant efficacy were published in 1995 by Mais et al., who applied ORC in 16 women undergoing laparoscopic endometriosis surgery [100] and in 25 women undergoing laparoscopic myomectomy,[101] respectively. Both treatment groups were compared to equally-sized untreated control groups. In the endometriosis study, Mais et al. evaluated the adhesion incidence, which was reduced by 63%. In the myomectomy study, the number of adhesion-free patients was evaluated, which was reduced by 48%. These reports did not provide more detailed results regarding adhesion extent or severity. Sekiba examined the use of Interceed® for infertility, as well as endometriosis surgery.[97] This study included 63 infertility patients, who underwent adhesiolysis surgery, and 28 women with severe endometriosis. In both populations, Interceed® was only used on one side of the pelvic cavity, while the other served as a control. The incidence of adhesion was reduced from 76% to 41% in the infertility surgery group and from 82% to 50% in the endometriosis surgery group. The fourth positive examination was performed in laparoscopic ovarian cystectomy patients.[102] In 17 patients, one ovary was treated with Interceed®, while the other served as an untreated control. Ovaries were free of adhesions in 13 of 17 patients in the Interceed® group vs. six of 17 patients in the control group.

Four publications described RCT outcomes where the ORC-treated group tended to achieve better results than the controls, but these differences were not statistically significant.

Tinelli et al. examined a not explicitly specified ORC barrier after intracapsular myomectomy in 694 women.[62] The rate of adhesions was decreased from 23% to 16% in laparoscopic surgery and from 28% to 22% in laparotomy. Wallwiener et al.[103] studied the effect of Interceed® in 20 women after endometriosis resection and compared them to 20 control patients without a barrier. They used a four-point adhesion score from 0 to 3, which was reduced from 1.1 to 0.4. Li and Cooke observed the effect of Interceed® after gynecologic adhesiolysis when hydrocortisone acetate solution (750 mg/30 ml) was instilled into the peritoneal cavity before closure.[104] They included 28 women, who had one side of the pelvic cavity covered with Interceed®, while the other was left untreated. They scored adhesion severity on a scale from 0 to 3, resulting in mean values of 0.9 for the controls and 0.7 for the intervention group. In addition, the extent of adhesion was measured; the mean was 38 mm^2 in the control and 16 mm^2 in the intervention group. The authors noted that the combined use of any intraperitoneal irrigants or instillants might possibly lead to the displacement of Interceed®.

In the fourth study with insignificant improvement, in 55 patients with bilateral ovarian disease, one ovary was wrapped with Interceed® while the other was left uncovered.[105] Adhesion severity was scored from 0 to 3. Adhesion severity was slightly reduced from 1.1 to 0.8 through Interceed® treatment and the adhesion area was reduced from 2.8 to 1.7 cm^2. The percentage of ovaries that developed adhesions was significantly reduced from 75% to 53%.

In the remaining four RCTs, ORC led to a worse outcome than the respective control groups, and in two of these (one against ePTFE and one against an untreated control) this deterioration was statistically significant. Saravelos and Li examined the application of Interceed® after standardized surgery for polycystic ovarian syndrome.[106] In 21 women with bilateral ovarian treatment, one ovary was covered with Interceed®, while the other was left untreated. The authors found that the incidence of adhesions with Interceed® treatment (43%) was 10% higher (not significant) than that in the control group (33%). Greenblatt and Casper [107] used the same approach in 8 women. They used the AFS score and obtained a mean score of 9.9 for the Interceed® side and 6.7 for the control side. Although the difference was not significant, it confirmed the negative findings by Saravelos and Li. In a study on prevention of the reformation of bilateral adhesions on ovaries, fallopian tubes, and fimbriae in microsurgical operations for fertility,[108] 66 women were treated with Interceed® on one

side, while the other was left as an untreated control. Adhesion severity scores (0 to 4) were ascribed to each ovary, fallopian tube and fimbria, respectively, during both interventions and mean aggregates were calculated to determine the difference between the first and second interventions; this was 4.9 in the control and 6.8 in the intervention group, which reflects a statistically significant worsening under treatment with Interceed®. The authors also noted that meticulous hemostasis should always be achieved before application. If Interceed® turns black after application, it has to be removed and hemostasis must be re-established. Only thereafter can a new piece of Interceed® be applied. As mentioned earlier, ORC gave statistically significant inferior results after gynecologic adhesiolysis compared to ePTFE.[95]

The aforementioned incompatibility of Interceed® with the presence of blood has also been described in more detail: clinical observations indicate that small bleedings are sufficient to allow blood to permeate the material, resulting in fibroblasts growing along the strands of the clotted blood, followed by collagen deposition, vascular proliferation, and finally adhesion formation through the barrier.[22,109] Related to this issue, it has been noted that use after myomectomy may be precluded as hemostasis at the myomectomy site is rarely complete.[110] In addition, in several animal studies, Interceed® failed to prevent adhesion formation.[91,111-116] In animal studies with intact peritoneum, application of ORC was shown to result in a sloughing of the mesothelial layer of the peritoneum, which is an obligatory injury to all contacting peritoneal surfaces and subsequent de novo adhesion formation. Possible explanations for this result include the acidity of the material, as well as activated leukocytes responsible for degradation, which may function as a cellular bridge leading to a common healing site and coalescing adhesions. Additionally, ORC elicits a peritoneal fluid inflammatory exudate characterized by large numbers of activated macrophages.[117] The authors assumed that these issues might be responsible for the inferiority of ORC compared to ePTFE. Histological analyses of adhesions formed despite the presence of ORC showed substantial amounts of Interceed® remnants in agglutination sites associated with a local inflammatory response.[91]

Hyaluronic acid

Hyaluronic acid (HA) is a natural component of the extracellular matrix that is also present in the peritoneal fluid.[118] Peritoneal mesothelial cells synthesize HA in vitro and it is thought to be involved in the regulation of fluid retention and the maintenance of structural integrity.[119] Hyaluronic acid has high water-binding capacities and forms a viscous gel after water absorption. Unmodified HA is subject to rapid degradation and is cleared from the site of administration within hours.[120]

The most commonly known product that used unmodified HA is the discontinued Sepracoat® by Genzyme (Cambridge, MA, USA). It was supposed to be applied, not after, but rather before and during surgery as a temporary protective coating to reduce tissue damage and the resulting adhesion formation. However, no gynecologic second-look RCTs using unmodified HA barriers have been published.

The rapid clearance rate that makes unmodified HA unsuitable for use as an adhesion barrier that prevents postsurgical contact between injured areas can be improved through crosslinking. Addition of ferric ions (Fe^{3+}) leads to ionic bond cross-linking with the carboxylate groups of the hyaluronate. This leads to increased viscosity and prolonged intraperitoneal residence time.

Direct comparison of the ionically cross-linked approach with unlinked hyaluronic acid in animal studies showed that ferric hyaluronate gel was more efficient than hyaluronic acid even when the concentration of hyaluronic acid was increased to match that of the ferric hyaluronate gel.[121] Products based on ionically cross-linked hyaluronic acid include Intergel by Lifecore Biomedical (Chaska, MN, USA), a gel made of sodium hyaluronate, ionically cross-linked with ferric ion (0.5%), and adjusted to isotonicity with sodium chloride solution. To date, three gynecologic second-look RCTs using ionically cross-linked HA gel have been published. In all cases, Intergel was used in patients undergoing peritoneal cavity surgery; they received either 300 mL of Intergel or RL as a peritoneal instillate at the end of surgery. Thornton et al.[122] used an adapted AFS score at 18 different sites in 23 women. Although the score was significantly reduced in the intervention group, the results were not given as numerical values, which complicates comparisons. Lundorff et al.[123] used the mAFS score to quantify adhesion development at 24 sites in 147 women. The score was significantly reduced from 1.3 to 0.5. Separate evaluations for the different kinds of procedures examined showed that the reduction was significant for adhesiolysis (from 1.7 to 0.6) and ovarian procedures (from 2.4 to 0.5), but not for myomectomies (0.8 vs. 0.3) or tubal procedures (1.5 vs. 0.6). Johns et al. followed the same approach in 265 women.[124] The median mAFS score was 2.3 in the controls and 1.3 in the intervention group (statistically significant). In addition to ionic cross-linking, there is also a possibility for covalent cross-linking of HA. This can be achieved without foreign molecules through condensation to form inter- and intra-molecular esters of HA, in some of the carboxyl groups are esterified with hydroxyl groups of the same and/or different HA molecules. This highly viscous product is called auto-cross-linked polysaccharide (ACP) gel. It also has a higher adhesivity and more prolonged residence time on the injured surface than unmodified HA [120] and is resorbed by the body after approximately seven days. Products based on auto-cross-linked hyaluronic acid include Hyalobarrier by Anika Therapeutics Inc. (Bedford, MA, USA) and HyaRegen® by BioRegen Biomedical Co. Ltd. (Changzhou, China). Liu et al. examined the latter in 215 women undergoing laparoscopic surgery for primary removal of adhesions, myomas, ovarian cysts, or endometriotic cysts.[125] Patients were evaluated using the mAFS score at 24 sites, which yielded a median of 0.9 in the saline solution-treated control group and a significantly lower value of 0.3 in the intervention group. Mais et al.[126] examined the effect of Hyalobarrier in 52 women undergoing laparoscopic myomectomy. A non-significant number of treated women were free of adhesions and the total adhesion score (Operative Laparoscopy Study Group Adhesion Score) was 2.1 in both groups. Several studies on intrauterine application of ACP found contradictory results concerning its efficacy at preventing adhesion, including positive [127-129] and negative [130,131] outcomes. ACP gel did not reduce adhesion formation in an animal peritonitis model,[132] an animal adhesion induction model,[133] or an animal ischemic button model.[134]

The blended HA-based product Medicurtain (Shin Poong Pharmaceutical

Co. Ltd., Seoul, South Korea) combines sodium hyaluronate with hydroxylethyl starch (HES). The latter is a pharmacological anti-coagulant that reduces the activity of several proteins in the coagulation cascade and increases prothrombin time and partial thromboplastin time.[135,136] Therefore, Medicurtain can only be applied when the application site is completely hemostatic, according to the product's instructions for use. No gynecologic second-look RTCs on the use of HA/HES-based barriers have been published.

Hyaluronate + carboxymethylcellulose (HA/CMC)

This approach uses a combination of two anionic polysaccharides, carboxymethylcellulose and hyaluronate (most commonly as sodium hyaluronate), which have been modified chemically. The mixture is available in different forms; as foils and as powder. HA/CMC transforms into a gel after being placed on the peritoneum, where it is reabsorbed within about 7 days.[137] A well-known and extensively studied preparation is Seprafilm® adhesion barrier by Baxter (Deerfield, IL, USA). As its foil form significantly hampers laparoscopic application, a powder that comes with a special spray applicator was developed under the name Sepraspray®, but it has apparently been discontinued. Fossum et al.[138] tested Sepraspray® after laparoscopic myomectomy in comparison to an untreated control. They included 41 women and used the mAFS score. They reported the scores as differences between the first and second interventions: 1.6 in the control and 0.7 in the intervention group, which were not significantly different. Although Seprafilm® has been studied extensively, most trials have been done in the field of general surgery, and only a very few have addressed gynecologic indications.[139] The only RCT was performed by Diamond,[140] who examined adhesion reduction after uterine myomectomy in comparison to an untreated control in 127 women. Both the mean uterine adhesion severity (1.9 vs. 2.4) and extent (1.2 vs. 1.7) scores were slightly but significantly reduced. Some safety concerns have been expressed regarding the use of Seprafilm®. In a comprehensive RCT in general surgery including 1791 patients, Beck et al.[141] found no difference in abscess incidence or pulmonary embolism; however, fistula and peritonitis occurred significantly more frequently in the Seprafilm® group than in controls. In a subpopulation of patients in whom Seprafilm® was wrapped around fresh bowel anastomoses, leak-related events, including anastomic leak, fistula, peritonitis, abscess, and sepsis, occurred significantly more frequently. In another controlled clinical study in general surgery, Cohen et al.[142] observed that infection complications (abscess and incisional wound complications) were significantly more frequent with glycerol hyaluronate/carboxymethylcellulose than in an untreated control group. Klinger et al.[143] reported intense peritoneal inflammation at the site of Seprafilm® placement and a corresponding foreign body granuloma reaction. Similar observations were reported by Remzi et al.[144] David et al. reported an inflammatory reaction caused by extensive adhesion formation, as well as a giant cell foreign body reaction towards Seprafilm®.[137] Furthermore, in several animal studies, Seprafilm® failed to prevent adhesion formation.[91,115,134] Furthermore, the handling of Seprafilm® has been described as a major limitation, since it is somewhat brittle and difficult to apply.[142]

Modified starch

Starch can be modified and cross-linked to improve its capabilities in medical applications. Most commonly, this is done to produce hemostatic devices, but there also is a product that combines this approach with the possibility for adhesion prevention, 4DryField® PH. It comes in the form of a powder and, when applied as such, it acts as a hemostat. It is hygroscopic and absorbs the watery components of blood, thereby concentrating enzymes and cells partaking in blood clotting, resulting in accelerated hemostasis. For adhesion prevention, it has to be transformed into a gel with sodium chloride solution. This can either be done extracorporeally, and then the gel is applied directly, or the powder is applied and then transformed in situ through dripping with an irrigation system. The amount of saline used can be varied, leading to gels of different viscosities adaptable to the specific requirements of the respective surgery. It is absorbed after approximately seven days,[145] which is the most obvious difference from starch-based hemostatic devices, which are all absorbed within the first 1-3 days. 4DryField® PH has been examined in a RCT after the resection of deep-infiltrating endometriosis in a second look design.[146] Adhesions were scored with regard to their severity and extent, with a score based on the AFS score, and the incidence was evaluated as well. The mean total adhesion score and the incidence were lower in the intervention group. The manuscript that describes this study is in preparation and the results will be published soon. A retrospective controlled study including 40 women who underwent adhesiolysis and, in some cases, resection of endometriosis and other pathologies, compared 4DryField® with an untreated control group. The results showed that the severity and extent of adhesions could be significantly reduced.[147] In gynecological studies without control groups, 4DryField® showed a distinct reduction of adhesion formation by 80% after the resection of endometriosis,[69] and by 85% after the resection of endometriomas.[148] Animal studies have also demonstrated that this product can reduce adhesions, with reduction rates in comparison to untreated controls of 88-100%.[149,150]. Additionally, a direct comparison to Interceed®, Seprafilm® and Adept® showed that it is significantly more efficient than any of these.[91]

Polyethylene glycol (PEG)

Polyethylene glycol has been used for adhesion prevention in SprayShield™ (Covidien plc, Dublin, Ireland), formerly SprayGel™ (Confluent Surgical Inc., Waltham, MA, USA), a two-component system consisting of two different polyethylene glycol-based fluids.[77] Furthermore, composite adhesion barriers have been introduced: Oxiplex/AP Gel or Intercoat®, a gel composed of polyethylene glycol and carboxymethyl cellulose, and REPEL-CV®, a polymeric film for cardiac surgery consisting of polylactic acid and polyethylene glycol.[151,152] The retention time of these products varies greatly, from about 5 to 14 days for SprayGel™ and SprayShield™[77] to 29 days for REPEL-CV [152] and 6 weeks or more for Oxiplex/AP Gel.[153] The results of three RCTs for SprayGel™ were promising. Mettler et al.[154,155] and ten Broek et al.[156] found a reduction of adhesion formation after myomectomy and in patients with different gynecological pathologies, respectively. According to a meta-analysis of the efficacy of SprayGel™ by ten Broek et al.[156] based

on the three aforementioned RCTs, the odds ratio was 0.27 (95% CI 0.11-0.67). In contrast, an experimental study by Rajab et al.[151] found only a minor difference in adhesion formation compared to an untreated control group. SprayGel™ was discontinued and replaced by SprayShield™, which is similar but slightly modified, including a different color and alterations that influence the time of absorption.[77] For SprayShield™, the results of only one RCT with second-look are available.[157] In this trial, SprayShield™ did not prevent adhesion formation, contradicting the promising results for its predecessor. Contradictory results have also been found in five RCTs on Oxiplex/AP Gel or Intercoat®. A slight decrease in adhesion scores between the first and second adnexal surgeries from 11.9 to 9.1 was found by Lundorff et al.[158] Here, the control group showed an increase in the mean adhesion score from 8.8 to 15.8, resulting in a significantly better adhesion score at second-look in the intervention group. Similar results were also obtained in a trial on endometriosis surgery by diZerega et al.[159] In that study, the mean adhesion score of adnexa in the intervention group slightly decreased from 8.4 to 6.2, whereas it increased from 10.0 to 14.0 in the control group. When comparing the adhesion scores from the second-look surgeries between the intervention and control groups, this difference was statistically significant.[159] In contrast, the results from an RCT by Young et al.[153] do not indicate a reduction of adhesion formation through the use of Oxiplex/AP Gel or Intercoat®. In this study, adhesion scores remained statistically identical between first (8.0) and second (8.1) surgeries. Only a slight, not statistically significant, advantage when comparing the second-looks of both groups was found, since in the control adnexa, the score somewhat increased from 8.0 to 11.6. Two RCTs on intrauterine application of Oxiplex/AP Gel or Intercoat® found contradictory results concerning its adhesion prevention efficacy, with positive[160] and negative[161] outcomes. The long resorption time of Oxiplex/AP Gel or Intercoat® and REPEL-CV raises concerns about possible foreign body reactions. In an experimental study with Intercoat®, marked redness of the peritoneal cavity and increased intraperitoneal fluid were found one week after application of the product.[162] This observation was confirmed histologically, indicating capillary dilatation and edema.[162] Although the authors also found increased mortality in mice after the application of high doses of Intercoat®, they assumed that this should not be a concern in humans.

DISCUSSION

Many different approaches to reduce post-operative adhesion formation have been developed. Since there is no standardized validation score, and indeed there are different adhesion classifications and distinctions in the interpretation of the results, a comparative assessment of the efficacy of the diverse adhesion prevention barriers is difficult.[163] We tried to tackle this problem by focusing on adhesion score results, but a direct comparison is still limited since these scores are not available in all studies. Even the main indicator, i.e., the statistical significance of the results, is not necessarily straightforward when two studies use different outcomes. Nevertheless, since most studies do provide adhesion score results and there are plenty of them in gynecologic surgery, it is still possible to obtain a clear picture of the efficacy of the relevant adhesion barriers.

Apart from its efficacy regarding tissue separation, an ideal adhesion barrier should persist for about seven days, be absorbed/metabolized without initiating inflammatory reactions, not be influenced by the presence of blood, and neither compromise wound healing nor promote bacterial growth.[140]

Although the solution form of icodextrin comes with the advantage of complete coverage in every case, convincing results are not available, as only one of the two RCTs yielded statistically significant results, albeit with only a slight difference between the two groups (11% improvement), and a main outcome was not commonly used. Overall, the principle of physical wound separation through (semi-) solid barriers outperforms the principle of hydroflotation. One of the main requirements for an adhesion barrier is that it should remain in place throughout the critical 7-day period of peritoneal healing.[140] Accordingly, the quick absorption of icodextrin solution from the peritoneal cavity can be assumed to be a major issue. When the product is gone by day four, the critical 7-day period for peritoneal healing is not entirely covered.

ePTFE-based membranes yielded remarkable results, with the highest reduction in all of the RCTs included with a score reduction of 87%, thus significantly outperforming ORC in a direct comparison. Nevertheless, they cannot be recommended for adhesion prevention: the huge drawback of ePTFE is the requirement of a subsequent surgery because it has to be removed.[33,164] Not only would this be an avoidable surgical intervention, it could again be a source for adhesion formation, diminishing its original efficiency. Therefore, ePTFE is not commonly used for adhesion prevention nowadays.

ORC only yielded mediocre results based on a comparison of the number of RCTs that found a statistically significant reduction (four) to the number without a significant reduction (eight). In addition, even in RCTs with significant results, the ORC groups showed a rather large degree of remaining adhesion formation and only one of them yielded more than 50% improvement. Also, ORC is the only material that showed a significant worsening when compared to an untreated control in a RCT. It has also been reported that Interceed® seems to aggravate rather than prevent adhesion formation if blood is present, and its effectiveness and safety have not been demonstrated in laparoscopic surgery.[140]

Hyaluronate-based barriers that included HA ionically cross-linked through Fe(III) seem to work better than those based on auto-cross-linked HA. Of the two ACP trials, only one gave statistically significant results and the briefly mentioned intrauterine trials showed inconclusive outcomes as well. The difference does not necessarily have to be due to the different cross-linking processes, since the low-viscosity gel of the former formulation is used as a cavity instillant with volumes of about 300 mL, while the latter is a gel of higher viscosity that is applied directly (and only) to the wound surfaces in small volumes of around 10 mL. The lower viscosity alone likely does not explain a better protective effect, indicating that the volume is an important factor that influences efficacy.

Both HA/CMC RCTs describe their application in myomectomy. Although one of these did not give statistically significant results, the small number of patients could have been a factor. In the other, larger RCT, a significant reduction was achieved. As Sepraspray™ has been

discontinued, the results with Seprafilm™ are of greater interest. However, with significant improvements of 21% and 29%, respectively, the corresponding RCT was only moderately successful. Furthermore, a Cochrane database systematic review from 2008 criticized the statistical analyses used in the study and suggested that the results should be interpreted with caution.[165] In addition, the decent coverage of very uneven surfaces with Seprafilm™ can be quite difficult, especially for the inexperienced surgeon, and it cannot be applied laparoscopically,[140] which severely limits its applicability.

The modified starch-based device 4DryField® gave remarkable results for an absorbable barrier. The possibility of using it as a combined product for hemostasis and adhesion prevention is intriguing and could be one of the factors that contributes to its promising outcome. The basis for adhesion formation is the development of fibrin strands and grids between two surgically injured sites. The main source of the fibrin is blood, which is why meticulous hemostasis is a cornerstone for effective adhesion prevention and why minor bleeding after surgery may limit the efficacy of anti-adhesion agents. This issue might be solved by the application of a modified starch-based powder for hemostasis. Accordingly, the combination of hemostasis and adhesion prevention in a single device is intriguing and of practical value.[166] Several different modified starch powder-based devices are available on the market, but, except for 4DryField®, there are all intended only for hemostasis. Considering the apparent similarity of these hemostatic agents, their use for adhesion prevention might seem promising. However, a recent study that directly compared 4DryField® to another starch-based hemostat, Arista™ AH (Becton Dickinson, Franklin Lakes, NJ, USA), showed that adhesion formation in the Arista™-treated group was not reduced, but rather equal to that in the untreated control group, whereas 4DryField® significantly reduced adhesion formation compared to both other groups.[149] The authors stated that starch-based hemostats generally do not have the capability to function as effective adhesion prevention devices and, instead, the effectiveness depends on the specific properties of the individual product.[149] This notion is supported by clinical results for another starch-powder-based hemostat, HaemoCer™ (BioCer Entwicklungs-GmbH, Bayreuth, Germany), for patients undergoing open and laparoscopic gynecological surgeries.[167] Like Arista™, HaemoCer™ was found to be ineffective in preventing adhesions.[167] The short retention time (only about 1-3 days) of starch powder-based hemostats like Arista™ and HaemoCer™ is likely to be an important reason for their reduced efficacy.

Of the seven RCTs that used different PEG-based barriers, only four achieved statistically significant results. As all three products mentioned here had a trial in which they failed to give a significant improvement, the proof of their efficacy is inconclusive. Improvement was between 30% and 58% with SprayGel™, which represents the best results among the PEG-based devices. While, on one hand, the easy applicability of PEG-based gels is an advantage, its long resorption time has the disadvantage of possible foreign body reactions. A further issue of products like SprayGel™ is the rather high cost.[33]

In general, adhesion barriers are usually tolerated well. No clear evidence of a negative influence on wound healing or promotion of bacterial growth has been found for any of the barriers described here. The possible, but rare, side effects of some of the products seem to be justifiable considering the possible benefits, as adhesion formation may have far more serious consequences. In addition, the use of an adhesion barrier does not considerably prolong surgery. Except for cases with extensive preparation requirements or, e.g., foil-like membranes that have to be rolled up to be applied through a trocar and then cautiously rolled out again, adhesion barriers can normally be placed quickly. Considering the patient's quality of life, more studies with secondary endpoint results, such as development of postoperative pain or fertility rates, would be desirable. However, the quantification of parameters like quality of life and pain remains difficult, as several other factors are relevant and the impact of remaining adhesion formation even in a case with significantly effective adhesion reduction remains unclear. Therefore, more emphasis on secondary endpoint results during follow-up, as well as the presentation of results so that they can be compared between studies are desirable. This would help make the diverse but diffuse risks resulting from post-operative peritoneal adhesion formation more tangible.

CONCLUSION AND OUTLOOK

The rationale for the routine use of adhesion prevention devices has been a subject of discussion for decades. To date, high efficacy is expected from Gore Tex Surgical Membrane and 4DryField®. The former device, however, is non-absorbable and its removal requires additional surgery. The latter device is a resorbable barrier. Intergel®, which is also absorbable, achieved an improvement of 43% to 54%. Secondary endpoint results regarding the severity of adhesion-related complications after barrier usage are still scarce and should be a focus of future RCTs. In general, the routine use of effective adhesion barriers in addition to adhesion-minimizing surgical practices is highly recommended, as adhesion prevention is pivotal and approaches other than barrier application fall short. A review of the economic impact of adhesions and their prevention has shown that the health care system benefits greatly from the use of effective adhesion barriers, which is associated with considerable cost savings. STI

AUTHORS' DISCLOSURES

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