

Postoperative adhesions and their prevention

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Introduction

That adhesions can form following abdominal surgery has been known since the beginning of surgery. Yet during the early years of surgery adhesion formation has received little attention, the focus being on infection and survival. In the seventies clinical endocrinology developed explosively, driven by the introduction of oral contraceptives and by the introduction of radio-immuno-assays, a technique that permitted for the first time the assay of reproductive hormones, and reproductive medicine and infertility became a subspecialty. Simultaneously reproductive surgery developed and the prevention of postoperative adhesion formation became important. Microsurgery was introduced¹, first as a magnification tool permitting tubal reanastomosis developing subsequently as a principle of surgery emphasizing the prevention of desiccation and gentle tissue handling.(fig 1) Prevention of adhesion formation was mainly based upon careful observational medicine and common sense, and most of the principles became only much later experimentally confirmed. Some mistakes, however were also introduced such as the free peritoneal graft to cover denuded peritoneal areas, a technique shown later to be strongly adhesiogenic².

The history of surgery and adhesion prevention cannot be viewed separately from the development of endometriosis and endometriosis surgery since cystic ovarian endometriosis is strongly associated with adhesion formation, and since endometriosis surgery is the most frequently performed fertility surgery. Diagnosis of infertility and of endometriosis and their treatment has driven the development of diagnostic laparoscopy complemented with minor laparoscopic surgical interventions and by microsurgery.

When lightweight endoscopic cameras were introduced in the mid eighties, endoscopic surgery developed explosively replacing progressively microsurgery and also laparotomy, not only in gynecology but also in abdominal surgery and in urology. This had important consequences for fertility and endometriosis surgery and for our awareness of adhesion formation. Until the early nineties fertility surgery with prevention of adhesion formation had remained centralized in highly specialized fertility centers^{3;4}. We then witnessed in parallel the increasing use and success of IVF and the development of more advanced endoscopic surgery such as deep endometriosis, bowel, pelvic floor and oncologic surgery. Reproductive surgery becoming

laparoscopic became mainstream surgery, the microsurgical focus on prevention of adhesion formation got lost. Indeed outside reproductive surgery, adhesion formation was widely considered as an unavoidable by-product of surgery, which could largely be prevented by good quality surgery. In retrospect, It is astonishing how fast the principles of microsurgery became by and large forgotten, with the overall belief that laparoscopic surgery was 'minimal invasive' surgery and thus even better than microsurgery and that adhesion formation would rapidly become a minor problem ^{5,6}.

With the realization that laparoscopic surgery was not the solution to prevent adhesion formation ^{7,8}, laboratory research on and clinical interest in adhesion formation revived, and new products were developed. Only in the last decade, we have become aware of the clinical importance of adhesion formation, mainly through the SCAR studies ⁹⁻¹¹. These clearly demonstrated that the incidences of bowel obstruction and of reoperation due to postoperative adhesions keep increasing linearly for at least 10 years and are much higher than anticipated. Also the awareness of postoperative adhesions as a cause of infertility and pain grew. With the awareness of the clinical importance we realized the associated costs, the market potential and the necessity of randomized clinical trials for new products. 'Quality of surgery' obviously being a key element in these trials, we realized that quality control of the individual surgical procedure is close to inexistent ¹², and videoregistration was introduced as a monitoring aid for these trials. Simultaneously came the awareness that 'quality of surgery' might be variable, that good quality surgery cannot be considered as universal with obvious consequences for the interpretation of adhesion formation statistics.

In conclusion, postoperative adhesion formation has never received the attention it deserves as evidenced by the absence of adequate keywords to search the literature. Only very recently the clinical importance has been acknowledged ¹³⁻¹⁷ stimulating research and the foundation of a dedicated society, the PAX society spanning gynecology and surgery.

Pathophysiology of adhesion formation

1. The mesothelial cell and the peritoneal cavity

Mesothelial cells form a monolayer resting on a basal membrane and an underlying connective tissue lining the organs and the wall of the abdominal cavity, of the pleura and of the pericardium. Mesothelial cells have been considered to be of mesothelial origin, but recently evidence has accumulated to consider that both these mesothelial cells and endothelial and hematopoietic cells are derived from a common progenitor cell originating embryologically in the splanchnic mesothelium¹⁸. More recently mesothelial stem cells have been described, which are able to differentiate to mesothelial cells, endothelial cells, smooth muscle cells, myofibroblasts, neuronal cells, adipocytes, chondrocytes and osteoblasts. In culture these mesothelial cells behave as epithelial cells, expressing mainly cytokeratin but under the influence of TGF β , HGF or EGF they transform into spindle shaped mesenchymal cells expressing mainly vimentin. It remains unclear what the relationship is between mesothelial stem cells and peritoneal repair following injury : indeed it remains debated whether these cells originate from the peritoneal fluid, from the mesothelium, from the submesothelial connective tissue, from the vascular endothelium or from blood cells. In any case, the concept of mesothelial stem cells is bound to be important for our understanding of peritoneal repair and of adhesion formation.¹⁹⁻²¹

The roles of mesothelial cells in maintaining normal serosal membrane integrity and function is still only partially understood. They secrete glycosaminoglycans and surfactant to allow the parietal and visceral serosa to slide over each other. They actively transport fluids, cells and particulates across the serosal membrane. They actively modulate gas resorption as CO₂ from the pneumoperitoneum^{22;23}. They synthesize and secrete mediators which play important roles in regulating inflammatory, immune and tissue repair responses, but we do not understand yet how these mesothelial cells communicate with each other and with surrounding cells, and what the role of progenitor cells is.²⁴

In the absence of ovarian activity peritoneal fluid is scanty. During the menstrual cycle peritoneal fluid is mainly formed as an ovarian transudate arising mainly from the developing

follicle or corpus luteum. Hence peritoneal fluid contains concentrations in steroid hormones that are much higher than in plasma. Mesothelial cells are highly specialized cells regulating the transport of fluid and proteins, especially those larger than 20.000 daltons, between the peritoneal cavity and the blood stream. For small molecules exchange is rapid by simple diffusion, but for larger molecules transfer is much slower. Thus concentrations of blood proteins as albumin, LH and FSH are more than 40% lower than in plasma, whereas locally secreted macromolecules as CA125 and glycodepins accumulate in peritoneal fluid with concentrations that are much higher than in plasma^{25-30 31} Peritoneal fluid contains high amounts of macrophages, which secrete, especially when activated, such as in endometriosis, a large variety of cytokines and growth factors. Peritoneal fluid thus is a specific micro-environment with protein and hormone concentrations which are much different from plasma.
32;33

When the mesothelial cell becomes traumatized (fig 3) , as demonstrated for hypoxia during CO2 pneumoperitoneum the large flat mesothelial cell retracts, known as 'bulging of cells', and the highly specialized layer of contiguous peritoneal cells is transformed into a layer of individual cells and between these cells large areas of basal membrane is directly exposed.³⁴⁻³⁹ Similar effects are believed to occur in response to all types of trauma such as dessication, mechanical or chemical trauma. The repair of this mesothelial cell trauma is rapid, and the peritoneal lining becomes normal again within 2 to 3 days. The consequence of this effect is largely unknown. Disruption of this highly specialized membrane is bound to affect all substances of which transport is actively regulated by the mesothelium layer. The resorbtion of CO2 from a pneumoperitoneum increases,^{22;23} whereas diffusion of larger molecules probably is greatly enhanced. It remains unclear to what extend this is associated with an inflammatory reaction and what the role is of attraction and activation of macrophages and their secretion products as cytokines and growth factors.

2. The classic model of Adhesion formation : a local phenomenon (fig 2)

A trauma of the peritoneum, involving besides the mesothelial cells also the basal membrane and the subendothelial connective tissue, is followed by a local inflammatory reaction,

exudation and fibrin deposition. This fibrin is normally rapidly removed by fibrinolysis⁴⁰ while simultaneously the peritoneal repair process is started⁴¹. Within hours after injury, the injured area is covered by what is believed macrophages and 'tissue repair cells, which within 3 to 4 days differentiate into mesenchymal cells. Repair starts specifically from numerous small islands and the repair of small and large areas therefore is similar. Given the concept of mesenchymal stem cells, the discussion about the exact nature of macrophages and tissue repair cells has acquired a new dimension, whereas the specific mechanism of repair starting from numerous small islands is easily understood.⁴² If the normal rapid repair of peritoneal lesions fails or when repair is delayed other processes which were activated become dominant. Within 4 to 6 days fibroblast proliferation invading the fibrin scaffold and angiogenesis start, leading invariably to adhesion formation. The importance of the fibrin scaffold between 2 injured surfaces was elegantly demonstrated since separating these areas by silastic membranes for up to 30 hours abolished adhesion formation⁴¹. This type of experiments, reinforced the belief that adhesion formation is a local process, that prevention should aim at separating the surfaces for at least a to 2 days, whereas medical treatment given intravenously or intraperitoneally has been considered less important since this type of treatment would have difficulties to reach the injured zone because of local ischemia and since it is shielded by the fibrin plug. The pathophysiology of this local process has been considered an inflammatory reaction, with players and mechanisms as fibrinolysis, plasmin activation and PAI's, local macrophages and their secretion products and the overall oxygenation of the area or the absence thereof, driving angiogenesis, fibroblast proliferation and mesothelial repair. The focus on macrophages and tissue repair cells is changing rapidly given the actual concept to consider these stem cells.

Other arguments in favor of viewing adhesion formation as a local process, are derived from the observations that some organs are more adhesiogenic than others and that this may be related to their fibrinolytic activity. A local process shielded from the rest of the peritoneal cavity seems also supported by the observation that normally peritoneal infection is kept localized by fibrin and adhesions. If not, a generalized peritonitis can become life threatening.

Little is known about the mechanisms which determine whether adhesions will be velamentous, thick and or vascularised and which factors determine innervations⁴³⁻⁴⁵. Also adhesion remodeling is something which is poorly understood.

3. The updated model : The peritoneal cavity as a cofactor (fig 3)

During the last decade evidence has accumulated that the entire peritoneal cavity can be a cofactor in adhesion formation^{7;22;23;46-59} Identified so far in laparoscopic rabbit and mouse models for adhesion formation are dessication, hypoxia, reactive oxygen species (ROS) and manipulation⁶⁰ which increase adhesion formation at an injured area. Since CO₂ pneumoperitoneum induced mesothelial hypoxia, results in the entire exposed peritoneal area in retraction of mesothelial cells exposing directly the extracellular matrix³⁴⁻³⁹, it is postulated that this results in the attraction into peritoneal fluid of substances of cellular elements, that enhance adhesion formation and/or^{22;23} decrease repair, without causing adhesion formation outside the injured area. For hypoxia by CO₂ pneumoperitoneum, or for dessication, one might argue that they also affect the injured site. The observation however of a similar dose dependent effect following manipulation of the omentum and organs outside the injured area, supports the concept that the entire peritoneal cavity can be a cofactor in adhesion formation.

It seems logical to postulate that any trauma to the large and flat mesothelial cells will induce them to retract as a defense mechanism, and that this effect is more pronounced when trauma is more severe. However, we do not know what the exact mechanisms are through which adhesion formation is further modulated. We only can speculate that macrophages and their secretion products, blood constituents or other inflammatory products affect directly the repair process or the differentiation of stem cells at the injured area. Any postulated mechanism should explain that desiccation enhances adhesion formation and that the effect is dose dependent. CO₂ pneumoperitoneum also enhances adhesion formation and the effect is pressure and duration dependent. The effect upon adhesions seems mediated through mesothelial hypoxia since the mesothelial layer stains hypoxic and since the increase in adhesions is prevented by the addition of 3-4% of oxygen (restoring the physiologic intraperitoneal partial oxygen pressure of 30 to 40 mm Hg), and is absent in mice partially

deficient for HIF1a and in HIF2a, hypoxemia response factor being the first to be activated by hypoxia. Similar effects are observed when partial oxygen pressures exceed 80 mm of Hg, thus increasing reactive oxygen species, and this effect can be prevented by oxygen scavengers.

4. Pathophysiology of adhesion formation : Conclusions

The classic model, that views adhesion formation as a local phenomenon (fig 2), and the effect of the entire peritoneal cavity (fig 3) and its constituents should be considered as complementary. The importance of each effect might moreover vary with the localization and the type of injury. Following severe traumas large areas as the pelvic cavity can become completely occluded by fibrinous adhesions and these areas probably escape from the influence of peritoneal fluid. In these circumstances, adhesion formation may follow mainly the classic model. For minor lesions especially non apposed lesions, as frequently occur during fertility surgery, the effect of the peritoneal cavity probably is dominant.

Both models also are important for our understanding of adhesions prevention agents. A flotation agent will also dilute peritoneal fluid and any factor secreted locally by the denuded areas, and will hamper the access of macrophages which cannot swim. Barriers on the other hand might in addition to keep tissues separated, shield the injured area from the peritoneal fluid and its constituents, something that might be beneficial or detrimental according to circumstances.

To understand the role of the mesothelial cells in peritoneal repair both models have to be considered simultaneously. Obviously peritoneal repair and adhesion formation between injured areas is a local process. The repair cells however, are at least partially derived from incorporation of free floating mesothelial cells in the peritoneal fluid, which today could be considered partially differentiated stem or progenitor cells. Since repair can be accelerated and adhesion formation decreased, by intraperitoneal injection and transplantation of autologous mesothelial cells, any deleterious effect to the peritoneal cavity is bound to affect these free floating cells. Today we only can speculate about endocrine or other factors affecting the function of these cells, and even about the sheer number of cells available for repair. It is unclear whether as a response to trauma of the peritoneal cavity by hypoxia or dessication, the

number of free floating mesothelial cells/stem cells are expected to be increased by attraction or to be decreased, since free floating cells could attach to cover the denuded areas in between retracted mesothelial cells. The importance of mesothelial cell and their differentiation is moreover highlighted by the observation that the fibroblast cultured from adhesions are permanently differentiated from other mesothelial fibroblasts⁶¹⁻⁶³, and by the observation that recurrence rates after adhesiolysis are much higher than expected.

Clinically some individuals form more easily adhesions after surgery than others, an observation supported by the fact that some mice strains form much more adhesions than others, while variability of adhesion formation is much lower in inbred strains⁵³. We also do not know why some adhesions are filmy and thin while other adhesions are dense; why *some* adhesions are vascular or avascular, or innervated or not.

Prevalence and clinical consequences of postoperative adhesion formation (fig 4)

Following abdominal surgery adhesions form in over 70% of women, and adhesions have been considered as a cause of infertility, pain and bowel obstructions. The clinical importance of adhesion formation has been emphasized by the SCAR study⁹⁻¹¹ demonstrating in a 10 year follow up of abdominal surgery in Scotland that the incidence of reoperation and of bowel obstruction kept rising almost linearly for a period of at least 10 years. Moreover re-interventions occurred in some 30%, in many persons more than once, and at least 6% could be linked directly to adhesion formation. Repeat surgery moreover was more difficult, more tedious and associated with more complications because of adhesions. From these findings models have been constructed, calculating cost of adhesions formation for society, and conversely the savings that could be realized by adhesion prevention assuming that reduction in adhesion formation could linearly be extrapolated to a reduction in pain, in infertility and in repeat surgery or bowel obstructions.

The real clinical picture, however, is not so clear. A first confounding factor is 'quality of surgery', which is variable. Duration of surgery and complication rates decrease by training as demonstrated in a series of learning curves in both the human and in animal models. Both the

duration of endoscopic surgery and the extent of manipulation have been demonstrated to directly affect adhesion formation. It must be recognized that in contrast with medical therapy for which quality control is strictly organized, there is no quality control for surgery¹². Further, there are no data available permitting to judge the importance of adhesion formation for fertility, not even after fertility promoting surgery. Moreover the results reported rather reflect centers of excellence and it is hard to judge whether differences in results are the consequence of techniques, indications or surgeons. Finally, the introduction of laparoscopic surgery probably has decreased overall the quality of fertility surgery. Indeed, during the 80's fertility surgery was performed in specialized centers by surgeons highly trained in microsurgery, who had an important clinical interest in adhesion prevention and who had developed the concepts of gentle tissue handling and moistening. The introduction of endoscopic surgery, a surgical access route used by most general gynecologists had as a consequence that generalists started performing fertility surgery, irrespective of training. That quality went down is difficult to prove given the absence of quality control in surgery, but the exponential rise in IVF cycles over the world might be due to some (major) extent to the decrease in the training and hence the use and quality of this type of surgery. If true, adhesion formation is a key factor.

That adhesions cause pain is widely believed based upon the observations that adhesions can be innervated^{45;64}, and that under local anesthesia, palpation of adhesions can cause pain^{65;66}. However, at present, we clearly cannot predict which adhesions cause pain, or whether adhesiolysis would be beneficial. Given this variability in the relationship between pain and adhesions, given the variable rate of adhesion reformation, it is not surprising that the results of adhesiolysis are still debated. Individual series have reported pain reduction, but this could be due to placebo effect after surgery, whereas the only RCT did not demonstrate a clear effect upon pain.⁶⁷

Prevention of postoperative adhesion formation (fig 5)

Adhesion formation between opposing injured peritoneal surfaces are acknowledged to be different from adhesion reformation following lysis of adhesions and from de novo adhesion formation outside the areas of surgery. Since, only adhesion prevention for the former has been investigated adequately, the following paragraphs will not discuss de novo adhesions and adhesion reformation.

1. Good surgical practice and conditioning of the peritoneal cavity

Good surgical practice and gentle tissue handling have been introduced as an important tenet by the pioneers of microsurgery. This comprised, moistening of tissues by continuous irrigation, moistening of abdominal packs, glass or plastic rods for mobilization of tissues, and precise micro-instruments. Reduction in adhesion formation was anticipated. However, it is only recently that the importance of prevention of desiccation and of gentle tissue handling have been proven, emphasizing how important and accurate clinical observation can be.

Key to good surgical practice today is whether the animal data can be extrapolated to the human. These data probably can be extrapolated since the effect of CO₂ pneumoperitoneum, the duration dependent increased CO₂ resorption, observed in mice and in rabbits, also occurs in women. Taking into account the findings in animal models, good surgical practice today should include the following. Firstly the insufflation gas should be conditioned in order to minimize hypoxia and desiccation; this requires humidification of the gas and the addition of 3 to 4 % of oxygen to the CO₂. Moreover, cooling of the peritoneal cavity is important since it decreases both the effects of hypoxia and of desiccation, cells being more resistant to metabolic damage at lower temperatures. Cooling of the peritoneal cavity moreover makes it possible for the humidified and saturated insufflation gas to condense upon entrance ~~of~~ to the pelvic cavity, thus preventing desiccation. Secondly the duration of surgery should be kept to a minimum, as well as the amount of bleeding and the extent of tissue manipulation. In summary the surgeon should be experienced and well trained.

Observation of strict sterility remains mandatory to prevent any kind of infection. This simple statement should be balanced against the observation that it is difficult to completely disinfect the umbilicus, and that each time the vagina is opened, at least some risk of infection occurs. This is even more likely with entry into the bowel. Good surgical practice therefore should begin by observing strictly sterile conditions. This might sound obvious but it is not so evident, since in endoscopic surgery many surgeons no longer wear masks, endoscopic surgery being considered a semi-sterile intervention. Looking carefully at endoscopic interventions many minor mistakes are noticed if judged by the standards of open surgery. Whether extensive

lavage following surgery might reduce adhesion formation or the risk of some minor infection is unknown. Following deep endometriosis surgery with full thickness resection and a bowel suture, extensive lavage with 8 liters clearly decreased the postoperative inflammation as judged by CRP concentrations while preventing late bowel perforations⁶⁸. This has stimulated us to extend the use of extensive lavage to all surgical interventions with an increased risk of infection such as following hysterectomy or salpingostomy for hydrosalpinx. Interestingly, microsurgery also emphasized lavage for removing clots, foreign substances and fibrin.

Taken together these measures of good surgical practice, and conditioning of the pneumoperitoneum, cooling and prevention of inflammation, should reduce adhesion formation by more than 60%.

2. Adhesion prevention in animal models

A wide range of products has been shown to be effective in animal models. Efficacy of all products described so far have been extensively investigated in our laparoscopic mouse model. It should be realized that in this model all criteria of good surgical practice as described are fulfilled, with standardized lesions, controlled duration of surgery, strict control of temperature and absence of desiccation. It should moreover be realized that the laparoscopic mouse model, is a model for three distinct pneumoperitoneum conditions, normoxia, hypoxia and hyperoxia. A first model intends to minimalise any peritoneal damage except for the lesions inflicted to induce adhesions. Thus, adhesions will form according to the classic model, with little or no effect of the peritoneal cavity. In this model 4% of oxygen was added to the CO₂ pneumoperitoneum to prevent mesothelial hypoxia. The second model is the 'hypoxia model, since adhesions are enhanced by CO₂ pneumoperitoneum induced mesothelial hypoxia. In this model pure CO₂ was used. In the third model, called hyperoxia model, 12% of oxygen was added to the CO₂ pneumoperitoneum, a concentration known to enhance adhesions probably by cell damage by reactive oxygen species.

Dexamethasone decreased adhesions by some 30% in the hypoxia model⁴⁷, by 60% in the hyperoxia model, and, especially, by some 76% in the normoxia model when it is combined with low temperature.. ROS scavengers decrease adhesions by 10 to 15% in both the hypoxia

and hyperoxia model, an effect too small to be demonstrated in the normoxia model, with much less adhesions to start with. Calcium channel blockers decrease adhesion formation by some 35% of inhibition in both hypoxia⁴⁷ and hyperoxia models, and around 58% in the normoxia model when is combined with low temperature; recombinant Plasminogen Activator (rPA) decrease adhesion formation by 40% in the hypoxia⁶⁹ and normoxia models whereas less inhibition, around 17%, was observed in the hyperoxia model. Ringers lactate as a flotation agent was marginally but significantly effective⁵¹. The effects of other flotation agents as carboxymethylcellulose (CMC) and Hyskon were marginal⁴⁶ (and surfactants as phospholipids gave some 35% of inhibition in the hypoxia and hyperoxia models and 58% in the normoxia model when is combined with low temperature. Icodextrin, (Adept, an 4% α 1-4 glucose polymer) unfortunately could not be evaluated since it degrades enzymatically in mice. Barriers as hyalobarrier gel, spraygel and Intercoat were highly effective in all models with a reduction of adhesions between 58 and 90%.

Prevention of angiogenesis also reduces adhesion formation, as demonstrated in PIGF knockout mice and by the administration of anti VEGF and anti PIGF monoclonal antibodies.^{55;56;61-63;70;71}

The transplantation of cultured mesothelial cells into the peritoneal cavity also is effective in decreasing adhesion formation^{72;73} and in remodeling the area of mesothelial denudation. More recently, mesothelial cells were used as transplantable tissue-engineered artificial peritoneum and research is focusing on the use of mesothelial progenitor cells.⁷⁴

3. Adhesion prevention in the Human^{46;47;69}

Adhesion prevention in the human has been limited to barriers and flotation agents with a reduction of adhesion formation that ranges, for all products, between 40% to 50%. Most important is that for none of these products efficacy has been proven for endpoints that really matter, i.e. pain, infertility, bowel obstruction or reoperation rate. We moreover should realize that large RCT trials were needed because of the high intra-individual variability, and that in these trials the surgical interventions were limited to rather simple and straightforward interventions as cystectomy and myomectomy. In addition, these trials have been performed

during interventions performed by laparotomy or by laparoscopy under conditions of CO₂ pneumoperitoneum enhanced adhesion formation and slight desiccation. It therefore is still unclear to what extent the available results of efficacy can be extrapolated to more severe or other types of surgery, and whether in the human the effect will be additive to good surgical practice and conditioning of the peritoneal cavity.⁴⁶

Sheet barriers as Seprafilm (Hyaluronic acid-carboxymethylcellulose)⁷⁵⁻⁷⁷, Interceed (Oxidized regenerated cellulose)^{78;79} and Gore-tex(Expanded polytetrafluoroethylene)⁸⁰ are proven effective but did not become very popular for various reasons. Seprafilm is difficult to use during laparoscopy whereas to be efficacious any remaining bleeding of the traumatized area should be avoided.

Since Intergel (0.5% ferric hyaluronate gel) has been withdrawn from the market, only Hyalobarrier gel(Auto-cross linked hyaluronic acid gel⁸¹), Spraygel (Polyethylenglycol) and Intercoat/Oxiplex^{82;83} remain available for clinical use. Overall efficacy appears to be similar for all 3 products. A comparison between these 3 gels can unfortunately not be made since comparative trials do not exist. Also the strength of the available evidence varies and a Cochrane review of hyaluronic acid and spraygel concluded that only for hyaluronic acid the evidence was solid.⁸⁴

Whereas in the human the efficacy of Ringers lactate as a flotation agent has not been proven, Adept,(Icodextrin)⁸⁵⁻⁸⁷ a macromolecular sugar with a higher retention time in the peritoneal cavity, was expected and shown to be efficacious in adhesion reduction. A major advantage is the safety and absence of side effects, which were well established since extensively used for peritoneal dialysis. The strength of the available evidence demonstrating efficacy, was in a Cochrane review not considered very solid.⁸⁴

Strong arguments can be found in the literature to use LHRH agonist prior to surgery as adhesion prevention⁸⁸ but specific clinical trials are lacking.

Discussion and a look to the future.

The concept of mesothelial cells as stem cells which can be transplanted to peritoneal trauma areas to modulate repair and decrease adhesion formation in animal models, is actually stimulating research aimed at collecting large amounts of autologous mesothelial stem cells and at manipulating them in culture prior to transplantation. Simultaneously, the addition to the peritoneal fluid of factors known to stimulate resident mesothelial proliferation or mobilization, or differentiation are investigated in order to decrease adhesion formation⁸⁹. Both the activation and multiplication of mesothelial cells is expected to be developed into new strategies to reduce postoperative adhesion formation.^{24;90;91} Also, the potential of using mesothelial stem cells derived from muscle is actively been investigated⁹².

Immense progress has been made over the last 15 years in our understanding of the pathophysiology of adhesion formation and the mechanisms involved. Besides the traditional concept viewing adhesion formation as a local inflammation with fibrin deposition and removal, the peritoneal cavity has been demonstrated to have an important role. Hence good surgical practice, gentle tissue handling, prevention of desiccation, hypoxia and ROS, and conditioning of the peritoneal cavity by cooling have become the first key aspects in prevention of adhesion formation. Since the mechanisms by which the peritoneal cavity influences adhesion formation remains unexplored we may reasonably expect that in the near future we will be able to decrease adhesion formation even further.

Inhibition of fibroblast proliferation obviously is an objective in adhesion prevention. The use of dexamethasone to reduce adhesion formation has been around since a long time but the efficacy has been debated and questioned. In our laparoscopic mouse model especially under conditions of minimal trauma to the peritoneal cavity the effectiveness was very pronounced. This was surprising, since other anti-inflammatory agents as COX1 and COX2 inhibitors were not effective. Therefore dexamethasone is suggested to be effective, not as an anti-inflammation agent but rather by inhibiting mesothelial proliferation. This is moreover consistent with the observations that dexamethasone reduces cell proliferation, collagen deposition and lung

fibrosis⁹³. The hormonal factors modulating fibroblast proliferation are being extensively investigated and hepatocyte derived growth factor (HGF), has been demonstrated to prevent peritoneal fibrosis.^{94;95} That HGF is also effective in reducing adhesion formation was demonstrated by transplantation of transfected mesothelial cells⁹⁶.

Since we understand that during adhesion formation different mechanisms are sequentially involved, adhesion prevention strategies should aim no longer at 1 mechanisms but a strategy addressing sequentially all different mechanisms should be considered. By doing so, we can decrease adhesion formation in animal models in over 90%. Prevention of adhesions will start with good surgical practice, and conditioning of the peritoneal cavity through cooling, prevention of desiccation and of hypoxia by adding 3 to 4% of oxygen. This will reduce adhesions by over 50%. If associated with ROS scavengers as vitamin C, and dexamethasone at the end of surgery adhesion formation in mice drops by an additional 30% ie to an 80 to 85% cumulative adhesion reduction. If at the end of surgery barriers are added, which by themselves are more than 50% effective, the cumulative adhesion formation reduction has been proven today to be more than 90%. Since the mechanisms through which the following products decrease adhesion formation are different from those listed before, we may expect that the effects will be additive. Indeed, effectivity between 30 to 40% was demonstrated for phospholipids and calcium channel blockers whereas drugs preventing neoangiogenesis by blocking PlGF of VEGF, are even more effective. This has not been demonstrated yet since in models where adhesion formation is already reduced by more than 90%, it becomes statistically difficult to prove additional effects. In conclusion, it seems reasonable to expect virtually adhesion free surgery in not too distant future.

Summary

We have been aware, for a long time that adhesions occur almost systematically in at least over 80% of women after abdominal surgery. The widely held belief has been that adhesion formation increases with the severity of surgery and with infection, but that this could largely be prevented by good quality surgery. Thus postoperative adhesion formation has for many years been emotionally ignored by the 'good surgeons'. Only in the last decade, we have

become aware of the clinical importance of adhesion formation, mainly through the SCAR studies ~~in~~ which have clearly demonstrated that the incidences of bowel obstruction and of reoperation due to postoperative adhesions keep increasing linearly for at least 10 years and are much higher than anticipated. That postoperative adhesions can cause infertility and pain, is well known, although quantitative data are missing.

Adhesion~~s~~ formation between traumatized areas has traditionally been considered as a local process, i.e. an inflammatory reaction, exudation and fibrin deposition followed by fibrinolysis and mesothelial repair. If the repair process is slowed down by infection, or very severe surgical trauma, locally insufficient blood supply, or foreign bodies such as sutures, a process of fibroblast proliferation together with angiogenesis starts and adhesions form. Key in this concept is that the fibrin is used as a scaffold for this process, and thus that without prior fibrinous attachment between surfaces, adhesions do not occur. Over the last decade, awareness has grown that secretions and/or cells from the entire peritoneal cavity strongly influence this local phenomenon. The factors identified so far are: desiccation, mesothelial hypoxia as it occurs during CO₂ pneumoperitoneum, ROS which occurs during open surgery, and mesothelial trauma as a result of grasping and manipulation of intraperitoneal organs. If judged from animal models this peritoneal effect is quantitatively much more important than the local phenomenon.

Prevention of adhesion formation therefore traditionally has focused upon good surgical practices~~s~~ and upon barriers or flotation agents or barriers preventing fibrinous attachments between injured surfaces. Flotation agents as Ringers lactate are marginally effective whereas Adept has claimed 40 to 50% effectiveness explained by an increased retention time. Mechanical barriers produced as sheets (Seprafilm, Interceed or Gore Tex) and gels (Spraygel, hyalobarrier gel, Intercoat) also have been shown some 40 to 50% effectiveness albeit for specific interventions performed by recognized good surgeons only. Most importantly [this is](#) a highly variable efficacy and it remains unknown, whether this variability in adhesions and in prevention, is patient or intervention or surgeon dependent. Anyway for none of these

products efficacy has been demonstrated for the clinically important endpoints such as pain, infertility or reoperation rate.

The concept emphasizing the importance of the peritoneal cavity has opened new approaches to prevention. Gentle tissue handling is getting a new dimension while during surgery the peritoneal cavity should be conditioned by preventing ROS, by preventing hypoxia by adding 3-4% of oxygen, by preventing desiccation and by cooling. In animal models these factors in combination are effective in reducing adhesions way over 80%. If used together with products as dexamethasone, and barriers an overall efficacy over 95% is obtained.

We only are at the beginning of understanding the mechanisms by which the peritoneal cavity affects adhesion formation. Whereas today the focus lies upon prevention of deleterious factors, we may focus on increasing the favorable factors, recognizing the importance of peritoneal stem cells in the repair process.

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List of legends

Fig 1. The pioneers of microsurgery, at a microsurgery workshop in Leuven, Belgium in 1978:
From left to right , Willy Boeckx, Ivo Brosens, Robert Winston and Victor Gomel (courtesy of I.
Brosens)



Fig 2 The Classic model of adhesion formation as a local process with trauma, exudation and fibrin deposition, fibrinolysis and rapid repair involving macrophages and tissue repair cells .

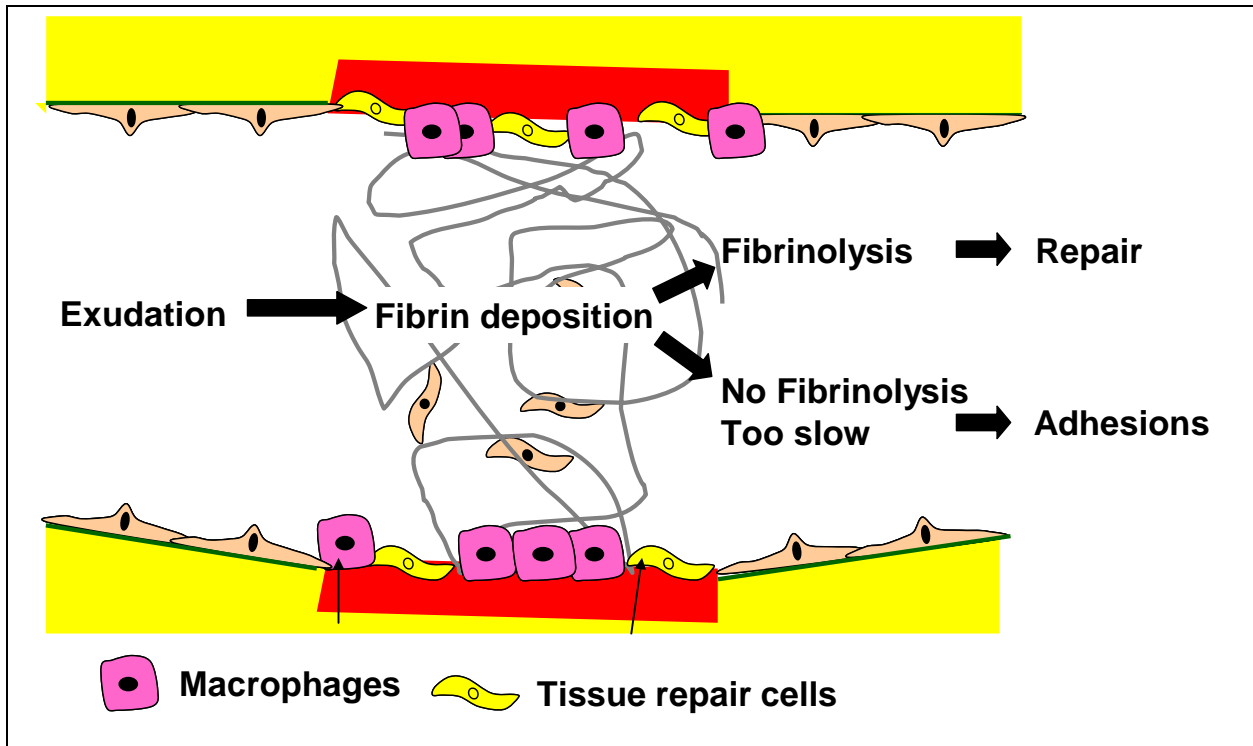


Fig 3 The updated model of adhesion formation. Flat mesothelial cells respond to trauma by retraction and bulging, exposing directly the extracellular matrix. The peritoneal fluid subsequently increases adhesion formation at the trauma site.

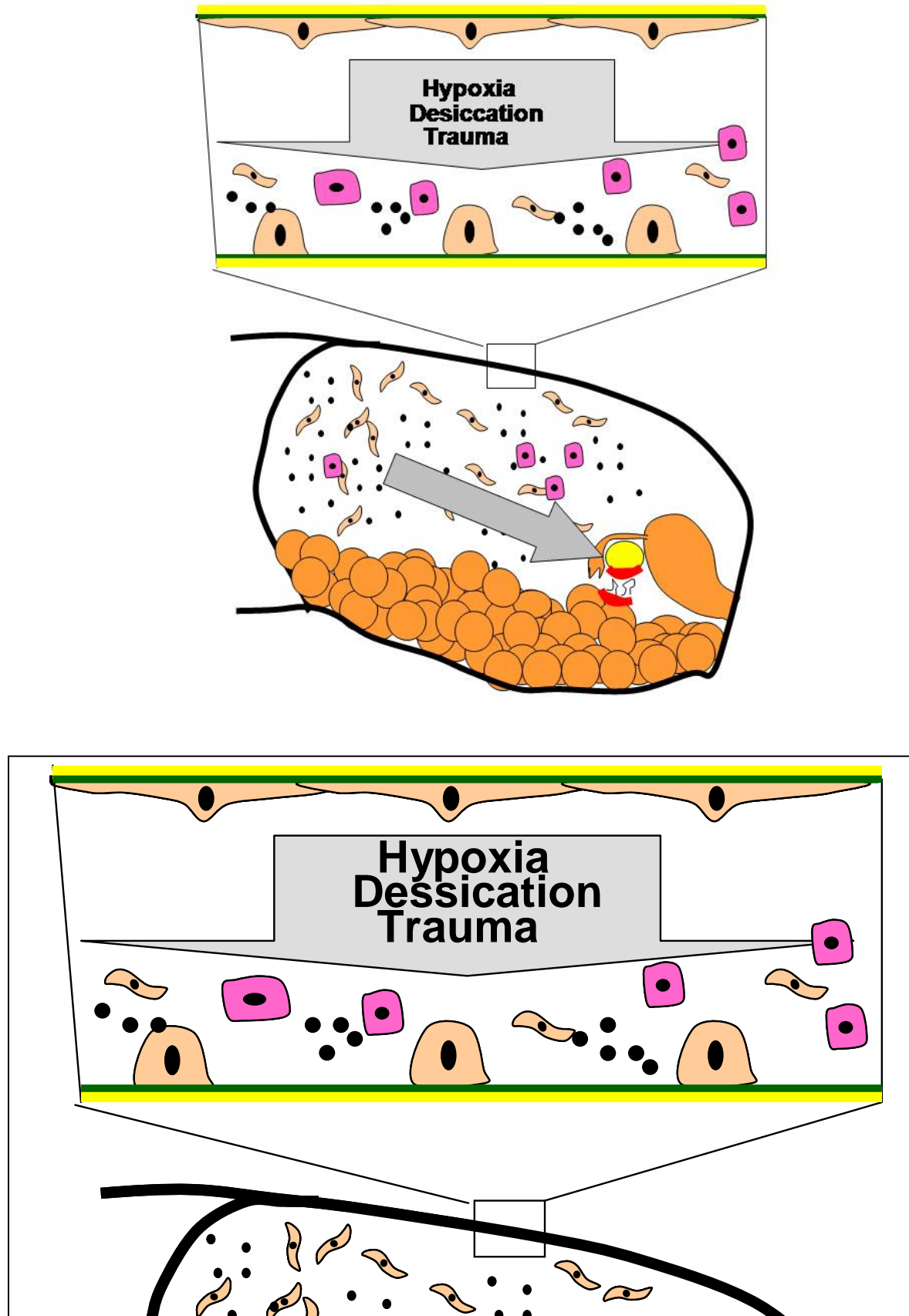


Fig 4 Clinical pictures of intraperitoneal adhesion

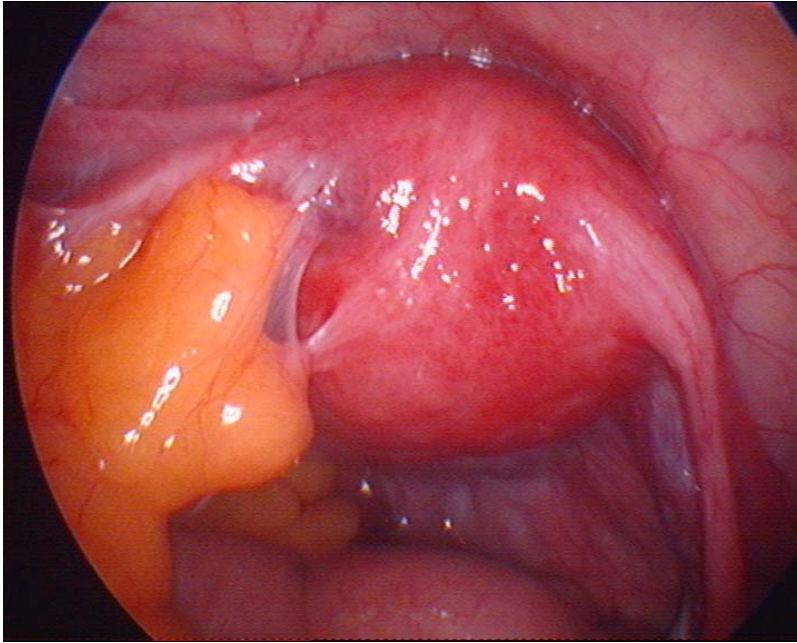
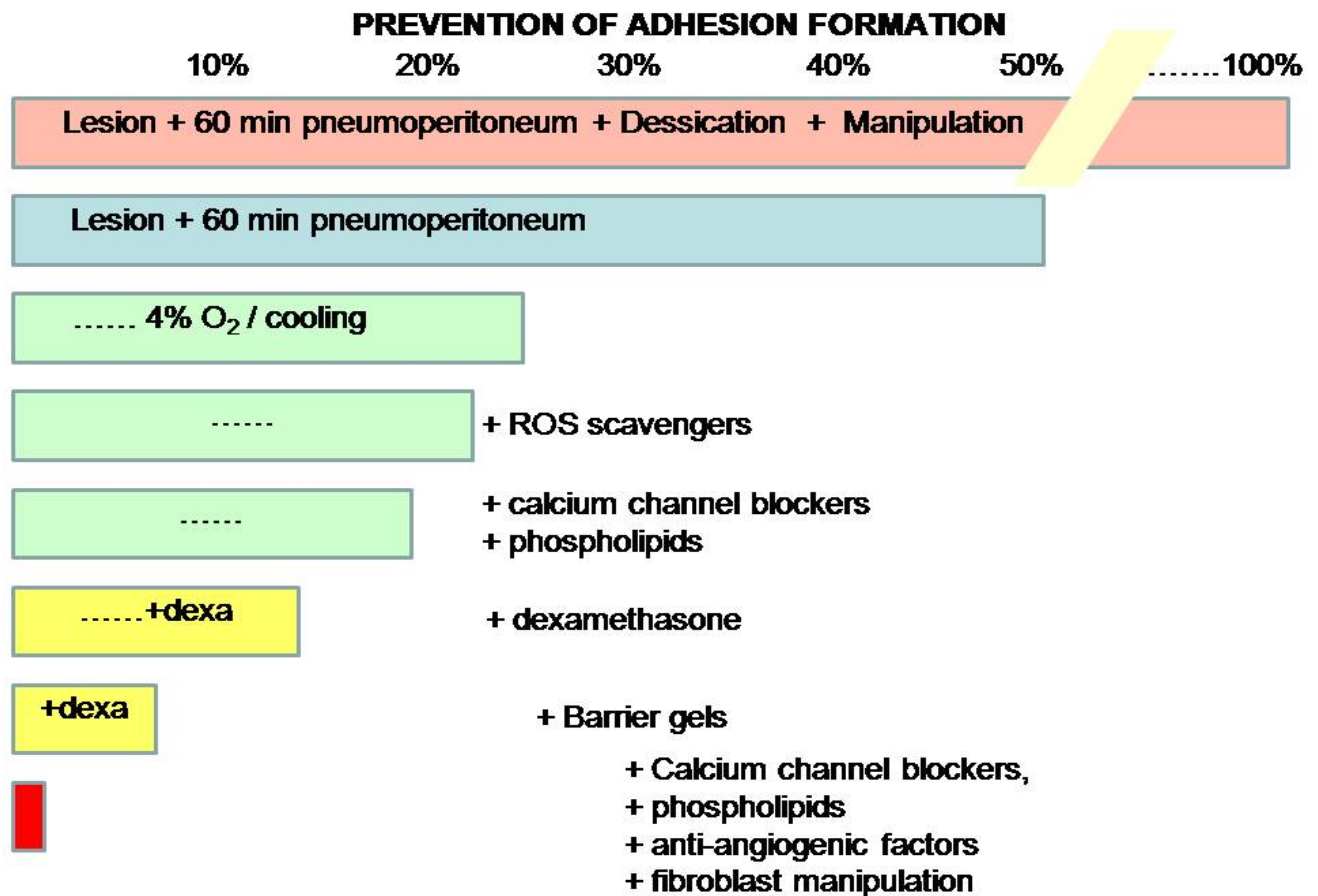


Fig 5 Prevention of adhesion formation anno 2008 in a laparoscopic mouse model. Minimalizing mesothelial damage by preventing dessication, gentle tissue handling, adding oxygen and cooling decrease adhesion formation to some 25%. Adhesions decrease further by adding ROS scavengers, calcium channel blockers, phospholipids or dexamethasone. In addition Barrier gels can be used achieving over 90% adhesion reduction. If in this model, calcium channel blockers, phospholipids, anti-angiogenic monoclonals and fibroblast manipulation would have additional effect close to 100% adhesion reduction might be achieved.



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