Chapter 23

Laparoscopic management and prevention of pelvic adhesions and postoperative pain

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INTRODUCTION

The consequences of pelvic surgery can include postoperative pain, adhesion formation, a recovery period, and postoperative fatigue.

For the same intervention, laparoscopic surgery is considered superior to laparotomy since it is associated with less pain, a faster recovery, a shorter hospitalization period, and a more aesthetic scar. Laparoscopic surgery moreover is also believed to be less adhesiogenic because the magnification of the surgical field and smaller instruments would permit a more precise surgery.

This chapter will present a mix of experimental data from animal models and observational medicine. We will emphasize the central role that acute inflammation of the peritoneal cavity plays in postoperative pain, adhesion formation, recovery, and fatigue. This should illuminate the pathophysiology of healing and recovery and thus aid in prevention of undesirable effects. In addition, this will highlight the differences between surgery by laparoscopy and by laparotomy, which requires a large incision in the abdominal wall.

The role of the peritoneal cavity might also give a glimpse of the future directions of surgery both for the patient's benefit and for the health care costs. These include both the direct costs of surgery and analgesics; and the indirect costs of recovery, fatigue, absence from work; and the costs related to adhesion formation such as chronic pain, infertility, reoperation, and possibly ovarian damage and tumor metastasis.

UNWANTED SIDE EFFECTS OF SURGERY

Postoperative pain, recovery, and fatigue

Pelvic surgery can result in both somatic pain, from the skin and wall incision(s), and visceral pain. Somatic pain results from nerve damage at the incisions site(s) and later from the inflammatory reaction that is necessary for healing.

Visceral pain is very different to somatic pain and involves specific nociceptors and specific neurotransmitters (Cervero & Laird 1999, Cervero 2009). At rest, these nociceptors are minimally reactive to a stimulus and they are more sensitive to stretch than to trauma. This explains why a full bladder can hurt more than a clean cut of a bowel. Inflammation of the pelvic cavity results in a rapid recruitment and activation of over 90% dormant nociceptors, which moreover will become much more reactive to any stimulus. Since pain results from the total firing activity while starting from a certain level of total firing activity onward, this explains why peritonitis causes even natural bowel movements to become very painful. The postoperative paralytic ileus thus could be considered a normal preventive mechanism to reduce pain, and the duration of paralytic ileus thus could be considered an indirect symptom of the severity and duration of the peritoneal inflammatory reaction.

The treatment of postoperative pain is limited to pain killers, which either reduce the inflammatory reaction or slow down the transmission of the pain stimulus to the brain. Pain killers vary from centrally acting morphine derivatives to NSAIDs and epidural anesthesia. Currently, no solution exists for the prevention of postoperative pain. The intraperitoneal administration of local anesthetics reduces pain for a limited period of time – 6 hours only (Greib et al. 2008, Park et al. 2010).

Postoperative pain, postoperative ileus, and the duration of recovery are associated with severity and duration of surgery. Duration of surgery is a predictor of duration of hospitalization and complications (Reames et al. 2014), and for the depression of the fibrinolytic system (Brokelman et al. 2009). Postoperative ileus is clinically considered to be related to the severity of surgery; however, the concept of postoperative ileus is poorly defined. Traditionally, fluid and food intake were restricted until first flatus, while bowel surgery required a bowel preparation. Recent developments cast doubt on the usefulness of a full bowel preparation and suggest early fluid and food intake in order to accelerate recovery (Mais 2014).

Postoperative fatigue (Kahokehr et al. 2011, Paddison et al. 2011, Zargar-Shoshtari & Hill 2009) following an abdominal intervention can last for up to 3 months in around 30% of patients. The mechanism is poorly understood but suggestive evidence relates postoperative fatigue to prolonged peritoneal inflammation (Paddison et al. 2008).

Although poorly understood, all evidence today points to an interrelationship between duration of surgery and postoperative complications, adhesion formation, and postoperative fatigue. It seems a logical hypothesis that postoperative pain, recovery, and fatigue have 'inflammation of the peritoneal cavity' as the common denominator.

Postoperative adhesions

Postoperative adhesions remain a major clinical problem. They occur in over 80% of patients and thus are the rule rather than the exception. That adhesions can cause mechanical infertility is self-evident.

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It is believed that around 30% of all infertilities are the consequence of adhesions.

Adhesions are believed to be the cause of chronic abdominal pain in 30% of cases. The relationship between the severity of adhesions and abdominal pain is unclear. Some minor adhesions can cause a great deal of pain and can be painful during traction under local anesthesia, whereas women with severe adhesions can be pain-free. Adhesions may contain pain receptors, in which case the mechanism for adhesion-related pain could be understood as the activation of specific nociceptors during bowel or body movements, which are mainly stretch or traction responsive. Adhesions cause close to 100% of all small bowel obstructions.

Following surgery, some women need a reintervention. As elegantly shown in the SCAR (Bhardwaj & Parker 2007, Ellis et al. 1999, Parker 2004, Parker et al. 2005, Parker et al. 2007, Parker et al. 2004, Parker et al. 2001) study, the incidence of reinterventions increased linearly for at least 10 years. By that time, around 30% of the women studied had undergone a reintervention, of which 6% were directly related to adhesions and 29% were probably related to adhesions. Adhesions can be the cause of reinterventions and of chronic pain. Adhesions are believed to be the direct cause of infertility (30% of the time), of chronic pelvic pain (30% of the time), and of nearly all postoperative bowel obstructions.

Economic burden of adhesions (Table 23.1)

The yearly number of bowel obstructions and interventions in **Table 23.1** were extrapolated from Belgian data. An estimation of the yearly cost of reinterventions likely to be due to adhesions was extrapolated from the cost in Scotland as calculated in the SCAR study. To estimate the yearly cost of infertility due to adhesions, we assumed that 30% of all yearly in vitro fertilization costs in Belgium were due to adhesions. This figure therefore is clearly an underestimation. To estimate the yearly cost of chronic pain, specifically due to adhesions, we consider this to be about one-third of the yearly cost of endometriosis.

In any event, postoperative adhesions constitute, in addition to the personal suffering of the patient, a huge financial burden on the health care system. This figure is even more impressive if the cost of postoperative pain, recovery, hospitalization, postoperative fatigue, and absence from work are taken into account.

PATHOPHYSIOLOGY OF ADHESION FORMATION

Surgical trauma

Peritoneal injury caused by surgery induces a series of well-timed local events at the trauma site starting with an inflammatory reaction, exudation, and fibrin deposition into which white blood cells, macrophages, fibroblasts, and mesothelial cells migrate, proliferate, and/or differentiate (DiZerega 2000a, DiZerega 2000b, Diamond et al. 2010). Within a few hours, the lesion is covered by macrophages and other 'tissue repair cells' although it is still unclear what their exact precursors are. Simultaneously, a race begins between fibrinolysis with mesothelial repair and proliferation of fibroblasts invading and proliferating into the fibrin mesh. Mesothelial repair starts from multiple islands, therefore large defects heal as rapidly as small defects. The healing of a mesothelial defect, starting from multiple islands, is rapid and almost finished by postoperative day two. If fibrin however persists longer because of continued inflammation (e.g. because of suture material) or because of a lengthier depressed fibrinolysis due to more severe surgery, the proliferating fibroblasts will use the fibrin as a scaffold to invade. This will initiate an adhesion which will be covered by mesothelial cells at the outside. If inflammation persists for >5 days, angiogenesis will be initiated and the adhesions will become vascularized and severe. The role of ileus is unclear.

Peritoneum and acute inflammation of the peritoneal cavity

The peritoneal cavity is a specific microenvironment different from blood. It is lined by large and flat mesothelial cells connected by gap junctions. Fluid in this cavity results from ovarian exudation during follicular maturation (Koninckx et al. 1980). The volume of peritoneal fluid thus increases exponentially during the follicular phase up to 400 mL. Since peritoneal fluid is ovarian exudate, it is not surprising

Table 23.1 Yearly adhesion-related procedures and cost for society

	Unit	Benelux	Europe	USA
Abdominal surgery	Number	1,928,450	34,615,425	21,327,554
Laparoscopic surgery	Number	964,225	17,307,713	10,663,777
Adhesion-related infertilities (30%)	Number	628,132	11,274,877	6,946,775
Adhesion-related chronic pain (30%)	Number	1,675,018	30,066,340	18,524,732
Adhesion-related bowel obstructions (100%)	Number	41,875	751,658	463,118
Adhesion-related cost of reintervention	€ (millions)/y	39	701	432
Adhesion-related chronic pain cost	€ (millions)/y	24	416	250
Adhesion-related fertility cost	€ (millions)/y	12	208	128

Adhesion-related reintervention costs were extrapolated from the cost of the SCAR study. The adhesion-related cost of infertility is an underestimation since extrapolated from the third of the yearly cost of in vitro fertilization in Belgium (assuming that 30% was caused by adhesions).

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that estrogen and also progesterone concentrations are several times higher than in plasma. Following ovulation with release of the follicular content into the peritoneal cavity, the concentrations of estrogen and of progesterone increase acutely and become around 1000 times higher than in plasma, decreasing progressively during the luteal phase (Koninckx, et al. 1980, Koninckx et al. 1980, Pattinson et al. 1981). The mesothelial cells actively regulate the transport of fluid and substances between the peritoneal cavity and the plasma. Transportation of molecules >60,000 Daltons is slow, explaining why concentrations of most plasma proteins such as lutein hormone, follicular stimulating hormone, prolactin, etc. are only 60% of the plasma concentrations, that clotting factors V and VIII are virtually absent, and that locally secreted large proteins such as CA125 and glycodelins are >100 times higher than in plasma (Koninckx et al. 1992). Also, macrophages and the immune system of the peritoneal cavity are specific, although less investigated. In women with endometriosis, natural killer cell activity is suppressed, whereas the peritoneal cavity contains more and more activated macrophages and their secretion products (Oosterlynck et al. 1992).

In addition to regulating transport of fluid, substances, and gases between the peritoneal cavity and plasma, the mesothelial cell facilitates gliding of moving organs such as bowels (and lungs and heart). Active regulation or inhibition of gas transport by the mesothelial cell is unexpected and unexplained, but it is the only hypothesis that can explain the observation that during CO_2 pneumoperitoneum in both humans and rabbits (Mynbaev et al. 2002a) the resorption of CO_2 increases progressively over time and that this increase is prevented by keeping the mesothelial layer intact through conditioning (Koninckx et al. 2013, Mynbaev et al. 2002b). In addition, intact mesothelial cells actively prevent the diffusion of nitrous oxide (N_2O) through the mesothelial layer since during N_2O anesthesia no N_2O can be measured in the pneumoperitoneum, and during pneumoperitoneum with 100% N_2O no N_2O can be measured in the lungs (Mulier & Van Acker, personal communication, 2012).

The mesothelial cell is extremely fragile and reacts very rapidly to any insult by retracting and bulging (Volz et al. 1999). This is best demonstrated by the fact that in vivo fixation in anesthetized animals is necessary to demonstrate the irritative effect of CO_2 pneumoperitoneum upon the mesothelial cell. The time to open the cavity and to take a biopsy will indeed induce severe alterations before fixation, which explains why human data on this subject is scanty and fundamentally unreliable. The retraction and bulging increase in line with the severity and duration of the insult. Additionally, within hours of insult to the mesothelial cell an acute inflammatory reaction initiates in the exposed area (Corona et al. 2011c). Repair of this mesothelial insult has not been investigated in detail, but these insults will always be repaired without adhesion formation. Indeed in none of the mice experiments performed was de novo adhesion formation observed. It is assumed that the acute inflammation in the human reflects postoperative C-reactive protein increase and peritoneal repair, which is finalized within a few days depending on the duration and severity of the insult.

Insults to the mesothelial cells leading to acute inflammation can be very subtle (**Figure 23.1**). Minor mechanical traumas such as gently touching and moving bowels can produce this response, providing yet more evidence to support the understanding that such surgical manipulation can be harmful (Schonman et al. 2009). These cells are extremely sensitive to hypoxia as superficially induced by a CO_2 pneumoperitoneum. They start retracting and bulging within minutes and the severity of the subsequent inflammatory reaction increases with the duration and the insufflation pressure of the pneumoperitoneum, at least up to 2 hours (Molinas & Koninckx 2000). They are equally sensitive to reactive oxygen species (ROS) as caused by exposure to >10% of oxygen or a partial oxygen pressure of >75 mmHg, the normal pressure in vivo being around 25 mmHg (Binda et al. 2007, Elkelani et al. 2004). Minor desiccation (Binda et al. 2006) rapidly causes ciliary beating to stop and more severe desiccation enhances the inflammatory reaction. Although not investigated in animal models or in the human, saline is known to cause rapidly cellular retraction of monolayer cultures (Polubinska et al. 2006). Also blood, both the plasma and to a lesser extent the red blood cells, strongly increases the inflammatory reaction in a dose-dependent manner (Corona et al. 2013).

The ultimate mesothelial cell trauma and the subsequent inflammatory reaction are the sum of all detrimental and beneficial factors. The trauma is moreover strongly temperature- or metabolism-dependent; temperatures >37°C exponentially increase the inflammatory reaction, whereas at temperatures <30°C the inflammatory reaction decreases by 50% (Binda et al. 2004).

Peritoneal acute inflammation: main factor in adhesion formation

From animal models, especially the mouse model, it became clear that adhesion formation following a surgical trauma was minimal without associated acute inflammation of the peritoneal cavity. Although a surgical trauma is necessary to initiate adhesion formation, the severity of the ultimate adhesion formation mainly depends on the severity of the acute inflammation in the entire peritoneal cavity (Corona et al. 2011c).

The adhesion enhancement at the local injury site has to be mediated by substances in peritoneal fluid, since manipulation of bowels

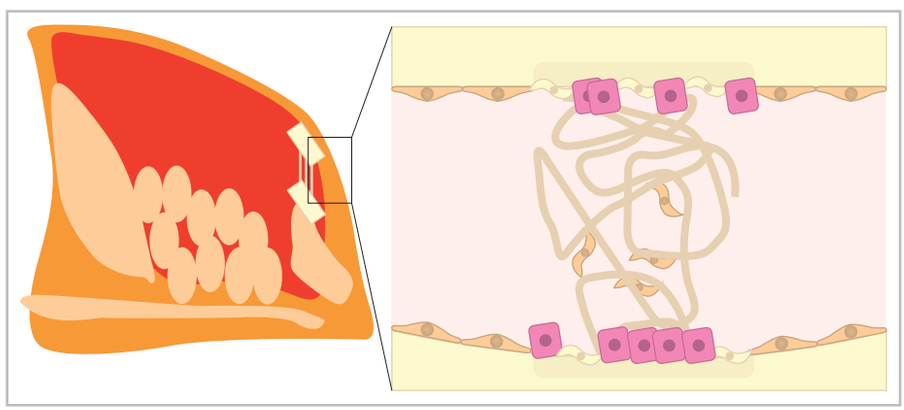

Figure 23.1 Insults of the mesothelial cells leading to retraction, bulging, and acute inflammation, and later to pain, CO_2 resorption, longer recovery, adhesion formation, fatigue, and probably tumor metastasis.

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in the upper abdomen can increase adhesions at surgical trauma sites in the lower abdomen (Schonman et al. 2009).

In humans, we only have indirect evidence that the same mechanisms occur. The relative importance of each factor in human surgery, however, remains to be established. Differences between animal models and human surgery are obvious: the duration of human surgery can be much longer, the surgical trauma much greater, the bleeding can be severe, and the rinsing of the abdomen varies widely in volume, temperature, and in composition of rinsing fluid.

PREVENTION OF ADHESION FORMATION

Gentle tissue handling with little bleeding

Gentle tissue handling was a paradigm of microsurgery. Gentle tissue handling seems logical, but in practice this was to prove difficult in humans. Animal models have shown that increased manipulation increases postoperative adhesions. Indirect evidence for the role of manipulation is derived from adhesion formation during learning curves: when performing identical interventions, expertise results in less adhesion formation (Corona et al. 2011a).

The adhesiogenic (Corona et al. 2013) effect of blood has been known for some time. The quantitatively important adhesiogenic effect of even 0.1 mL of blood, however, came as a surprise – as demonstrated in mice models. That plasma is more adhesiogenic than red blood cells points to the effect of fibrin and the resulting inflammatory reaction. This suggests that the use of some heparin in the rinsing fluid should result in a reduction of fibrin deposits. The effectiveness of heparin however has never been demonstrated, neither experimentally nor clinically.

Prevention of acute inflammation

Prevention of acute inflammation obviously consists of avoiding all factors that are recognized as harmful for the mesothelial cell and therefore cause retraction, bulging, and acute inflammation.

- The duration and quality of surgery are important. It has been demonstrated in animal experiments that adhesion formation increases with the duration of pneumoperitoneum – the duration of surgery in humans has also been recognized as an important cofactor (Trew et al. 2011). In humans the duration of surgery is dictated by the type and complexity of the intervention, so the expertise of the surgeon becomes a key factor in adhesion formation by decreasing manipulation and operating time.
- It is important to maintain a normal physiologic partial O_2 pressure of the mesothelial cell. The addition of 4% O_2 to the CO_2 pneumoperitoneum results in a partial oxygen pressure of 28 mmHg. The same holds true for open surgery where the addition of 4% of O_2 to either CO_2 or a neutral gas such as N_2 will prevent ROS production because of the oxygen concentration, which is 20%.
- Desiccation should be avoided by humidification of the gas.
- The temperature of the peritoneal cavity should be kept <32°C so that it achieves 80% of the beneficial cooling effect. However, the peritoneal cavity can be cooled to some 25°C, which in the absence of desiccation will not affect core body temperature (Corona et al. 2011b). Cooling of the peritoneal cavity obviously has to be done with a third means, and cannot be done with the gas used for the pneumoperitoneum. Insufflating humidified but cool gas will result in desiccation since the water content of cold gas is much less, and also this gas will be heated in the peritoneal cavity by the body.

The single most effective factor, however, is the addition of >5% of N_2O to the pneumoperitoneum. In animal models, N_2O has a half maximal effect at a concentration of 2.5% and a full effect from 5% onward as demonstrated for 100% N_2O (Corona et al. 2013, Koninckx et al. 2014). This points to an unknown drug-like effect of N_2O, although the mechanism of action is unknown.

Dexamethasone, 5 mg after surgery, has been used for many years but results were inconsistent. In animal models, however, after full conditioning, i.e. elimination of detrimental factors for the mesothelial cells, dexamethasone is highly effective in decreasing the remaining adhesion formation by 30%. The mechanism is unclear but could be the prevention of a proliferation of fibroblasts or a decrease in inflammatory reactions (Binda & Koninckx 2009).

In this context, it is important to recognize that in animal models anti-inflammatory drugs such as antitumor necrosis factor-α, and Cox I or Cox II inhibitors do not affect adhesion formation. A series of other factors slightly decrease adhesion formation in animal models but they are without direct application to the human. These comprise ROS inhibitors and vitamin C, calcium channel blockers, and antiangionetic factors as monoclonals against VEGF (vascular endothelial growth factor) or against PlGF (placental growth factor).

Barriers

Adhesion formation has been considered a rapid and local process between two opposing lesions (**Figure 23.2**). Prevention of adhesions therefore was based on the principle of keeping two opposing lesions separated for at least 5 days with resorbable solid or semisolid barriers such as Interceed or Intercoat of Johnson & Johnson, Spray-shield of Covidien or Hyalobarrier gel of Nordic, or with flotation agents such as Adept of Baxter. All "of these" ? substances are chemically hydrolysable polysugars with a minimal local inflammatory reaction. Since they are hypertonic, they all induce some local edema. The major technical problem is to keep these semisolid gels in place after application. The efficacy of these products ranges between a 40% and 50% reduction in adhesions, as demonstrated after minor interventions such as ovarian surgery or myomectomies. The variability in final adhesion formation is high, but this is probably due to the interindividual variability in sensitivity to adhesion formation.

None of these products are FDA approved, apart from Interceed and Adept. In Europe, these products were licensed to be marketed based upon (limited) safety data and the absence of serious side effects.

Quantitative efficacy of adhesion prevention

Efficacy in animal models

The efficacy of each individual factor could obviously only be investigated in animal models for ethical reasons. Adhesion formation after a well-performed laparoscopic surgery with humidified CO_2 is taken as a point of reference to compare the effect of the different factors affecting adhesion formation. Adhesions can be increased at least 2- to 10-fold by traumatic manipulation, excessive desiccation, and by blood.

The addition of >5% of N_2O to the CO_2 pneumoperitoneum will decrease adhesion formation by 60–70%. Although the addition of a few percent of O_2 has some beneficial effect when used alone, an additive effect when used together with N_2O could not be demonstrated. If the peritoneal cavity is cooled further to around 30°C, adhesion formation

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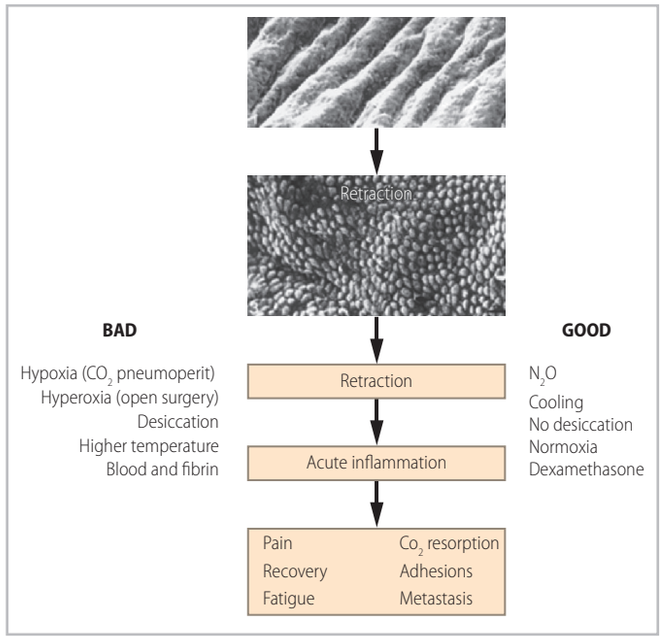

Figure 23.2 The classic model of adhesion formation between opposing lesions. Fibrin and fibrinolysis have a crucial role.

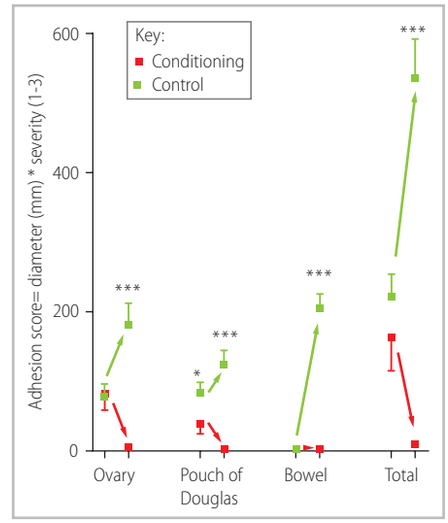

Figure 23.3 Adhesion score before surgery and at repeat laparoscopy in the full conditioning and in the control group, around the ovaries, in the pouch of Douglas (between uterus, rectum, and rectosigmoid), between bowels and side wall together with the total score (mean and standard error of the mean). Reproduced with permission from Koninckx et al. (2013). *, $P<0.05$; ***, $P<0.001$.

will further decrease to 85–90%. If, in addition to N_2O and cooling, a barrier is added, adhesion formation will be prevented by virtually 100%.

Efficacy in humans

First of all, it should be emphasized that all trials in adhesion prevention have been done by surgeons who were aware of the problem of adhesions, and thus the first assumption of good surgery by experienced surgeons has always been met.

After minor interventions such as ovarian surgery or myomectomies, barriers have an efficacy between 40% and 50%. Comparative trials between barriers to the best of our knowledge have not been performed. The interindividual variability in final adhesion formation is high, but this is probably due to the individual variability in sensitivity to adhesion formation.

In a randomized-controlled trial in severe deep endometriosis surgery, a protocol including: the addition of 10% N_2O to the pneumoperitoneum, together with cooling the abdominal cavity to 30°C without desiccation, 5 mg of dexamethasone, and a barrier (Hyalobarrier gel) at the end of surgery, was close to 100% effective. In the control group, adhesions were high (Koninckx et al. 2013) (**Figure 23.3**).

Unfortunately, because of the difficulty of performing repeat surgery to assess adhesion formation, all series on this subject are small. There are no data that demonstrate safety after bowel surgery, efficacy after severe interventions or that demonstrate a reduction in clinically important end points such as reoperation rate, chronic pain, or fertility.

LAPAROSCOPIC MANAGEMENT OF ADHESIONS

Laparoscopic adhesiolysis is not different from adhesiolysis during open surgery. The technical difficulty varies from easy velamentous adhesions to difficult dense adhesions, and the risk of bowel lesions can become real. During surgery, the surgeon therefore has to balance the difficulty and the risk of an adhesiolysis with the expected benefits of an adhesiolysis. An adhesiolysis can be necessary to gain access to the pelvis or an adhesiolysis can be useful to relieve pain.

The creation of a pneumoperitoneum (Tulandi et al. 2011) in women suspected of adhesions can be difficult. If periumbilical adhesions are expected, Palmer's point should be used. A detailed discussion of entry technique is beyond the scope of this article. Ultrasonographic evaluation of adhesions to the anterior abdominal wall, especially the umbilicus, seems promising. Unfortunately the efficacy has not yet been demonstrated adequately.

Adhesiolysis of adhesions between the anterior abdominal wall and bowels or omentum can be technically difficult mainly because of limited access. Personal experience has demonstrated that a CO_2 laser used through an operative laparoscope has a clear advantage due to visibility, manipulation, and angle of cutting. The major challenge of managing adhesiolysis remains the prevention of adhesion reformation. Unfortunately, few studies have specifically addressed this, and the overall recommendation is the same as for general prevention of adhesion formation.

ADHESIONS, THE LARGER PICTURE AND CONCLUSIONS

Peritoneal repair and adhesion formation can be considered as a race between mesothelial repair and fibroblast growth over the course of a few days, with the duration of persistence of fibrin and fibrinous attachment between organs and the inflammatory reaction in the peritoneal cavity as important modulating players. Many aspects however remain unclear (De Wilde et al. 2014).

Genetics and fibroblasts

In mice and in humans (Tulandi et al. 2011), the genetic constitution has an important role in adhesion formation. Some strains of mice, such as BALBc mice, are highly adhesiogenic and are therefore used for research in adhesion formation. The reason why it is hard to induce adhesions in other strains is unknown. When strains of mice that are strongly adhesiogenic, are bred with mice that are much less adhesiogenic, the offspring has an adhesiogenicity that is roughly the mean of both parents. This strongly suggests underlying genetic differences. Women with keloid formation have more adhesions. It can only be

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speculated whether this is caused by genetic differences in fibrinolysis, fibroblast proliferation, or inflammatory reaction, and cytokines or stem cells for repair. The mice model is the perfect model to identify differences at the level of the genome, and further investigation of this could lead to new methods of adhesion prevention in the future.

A series of experiments by M Diamond (Ambler et al. 2012, Diamond et al. 2011, Shavell et al. 2012) in animal models and in humans clearly demonstrates that fibroblasts from adhesions are different from normal fibroblasts, leading to the concept of dedifferentiation of fibroblasts in adhesions. This concept could have important clinical implications. It could explain why adhesion reformation after adhesiolysis is so important, and why adhesion reformation increases with repetitive adhesiolysis. Unless the underlying mechanisms are understood, the clinical message is that repetitive adhesiolysis should not be performed (or at least should be considered carefully), and that adhesion excision with removal of the 'bad' fibroblast would be preferable to adhesiolysis.

Duration of surgery

The duration of surgery increases the infection risk, duration of hospitalization, and complications for identical interventions in bariatric laparoscopic surgery (Reames et al. 2014) and adhesion formation. A combination of the effects of learning curves, and the concept of peritoneal inflammation that increases with duration of CO_2 pneumoperitoneum, led to the duration of surgery being one of the significant covariables in the GENEVA trial (Trew et al. 2011).

Inflammation of the peritoneal cavity as a key mechanism

The peritoneal fluid has a specific microenvironment, and the role of fibroblasts as active regulators of the homeostasis of the peritoneal cavity that modulate not only the transport of liquid, ions, proteins, gases, and cells but also macrophages and natural killer cells has been well documented. The peritoneum, with its huge area of over 10 m^2, and the peritoneal cavity should be considered as a specific organ that serves specific functions. The mesothelial cells help the gliding of moving bowels with the help of phospholipids. It should be realized that the hormonal and immunologic environment of regurgitated endometrial cells and superficial endometriosis is not plasma but the peritoneal fluid with much higher steroid concentrations and different cytokines. The cavity reacts to infection by isolating the infection through ileus and adhesions in order to prevent a generalized peritonitis.

Only recently we realized the speed of retraction of the mesothelial cells in response to different injuries. The quantitative relationship between the severity and duration of injury and the duration and severity of the subsequent acute inflammatory reaction and of the subsequent changes in composition of the peritoneal fluid is poorly understood today.

In the process of injury repair versus adhesion formation, the peritoneal fluid has an important role. An injury without associated acute inflammation of the peritoneal cavity causes little or no adhesions. The severity of the acute inflammation of the peritoneal will enhance adhesion formation at a trauma site and is quantitatively the most important factor in adhesion formation. This is not that surprising considering the physiologic protective survival mechanism of isolating an infection in order to prevent a dangerous generalized peritonitis. It is unclear to what extent the postoperative decreased bowel movements will contribute to adhesion formation, and whether earlier postoperative bowel movements are protective against adhesion formation.

Endometriosis is associated with a chronic low-grade inflammation with more and more activated macrophages, often with few symptoms. This probably explains pain, chronic fatigue, and discomfort. Similarly, it is postulated that a more prolonged acute inflammatory reaction of the entire cavity could explain postoperative pain, chronic pain, and fatigue (Wang et al. 2012).

Prevention of acute inflammation through conditioning

We are only at the beginning of identifying the surgical insults to the mesothelial cells. CO_2 pneumoperitoneum increases the severity of acute inflammation and this effect is duration- and pressure-dependent through a mechanism of superficial cellular hypoxia and less through pH changes. Besides ROS and a partial oxygen pressure of >75 mmHg (>10%), desiccation and absence of blood are important.

Prevention of acute inflammation thus begins with an experienced surgeon combining a shorter duration, minimal manipulation, and little bleeding. During surgery, the addition of a little N_2O, possibly O_2, cooling without desiccation and dexamethasone are important. Interestingly preoperative dexamethasone accelerates recovery and postoperative fatigue following cholecystectomy (Murphy et al. 2011, Zargar-Shoshtari & Hill 2009).

Prevention of acute inflammation strongly reduces pain during surgery, reduces CO_2 adsorption and metabolic acidosis, and reduces adhesions by about 85%. It is expected that this also will reduce postoperative fatigue (Kahokehr et al. 2011), tumor cell implantation (Binda et al. 2014), ovarian damage, and leaks after bowel surgery. It is unclear to what extent the faster recovery of bowel movements and metabolism plays a role.

If together with conditioning, a barrier is also used, surgery becomes virtually adhesion-free. This indirectly confirms that adhesions are formed as a local process, which is modulated by substances from the peritoneal cavity.

Barriers are important as an additive

It is logical to offer barriers that keep opposing surfaces separate. Tissue repair and adhesion formation is a rapid process and experimental data has shown that 5 days is considered to be sufficient for the process of adhesion formation to be completed. In humans, the efficacy of adhesion barriers ranges from between 40% and 50%. It is unknown whether the mechanism of action is purely mechanical or if these barriers also restrict contact between the surgical surfaces and peritoneal fluid.

Flotation agents

Flotation agents have been useful in adhesion prevention in humans for some time. In mice models, a slight but significant improvement in adhesion prevention could be demonstrated by Ringer's lactate. It has been suggested that this agent keeps surfaces separated, but the mechanism could equally be a dilution of peritoneal fluid with a decreased effect in adhesion enhancement.

The role of Adept as a flotation agent is unclear. The clinical efficacy is limited, which is not surprising with recent data on the retention time. The resorption is exponential and the retention time is only slightly higher than that of Ringer's lactate following use.

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