Prevention of adhesions in gynaecological endoscopy

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Adhesions resulting from gynaecological endoscopic procedures are a major clinical, social and economic concern, as they may result in pelvic pain, infertility, bowel obstruction and additional surgery to resolve such adhesion-related complications. Although the minimally invasive endoscopic approach has been shown to be less adhesiogenic than traditional surgery, at least with regard to selected procedures, it does not totally eliminate the problem. Consequently, many attempts have been made to further reduce adhesion formation and reformation following endoscopic procedures, and a wide variety of strategies, including surgical techniques, pharmacological agents and mechanical barriers have been advocated to address this issue. The present review clearly indicates that there is no single modality proven to be unequivocally effective in preventing post-operative adhesion formation either for laparoscopic or for hysteroscopic surgery. Furthermore, the available adhesion-reducing substances are rather expensive. Since excellent surgical technique alone seems insufficient, further research is needed on an adjunctive therapy for the prevention and/or reduction of adhesion formation following gynaecological endoscopic procedures.

Key words: adhesion/endoscopy/prevention

Introduction

Adhesions are defined as abnormal fibrous connections joining tissue surfaces in abnormal locations (Baakdah and Tulandi, 2005) usually due to tissue damage caused by surgical trauma, infection, ischaemia, exposure to foreign materials, etc. (Diamond and Freeman, 2001).

Diamond and Hellebrekers divided adhesions into two types, primary or de novo adhesions (those that are freshly formed, on locations where no adhesions were found before) and secondary or reformed adhesions (those adhesions that undergo adhesiolysis and recur at the same location). (Diamond et al., 1987; Hellebrekers et al., 2000). Additionally, in gynaecology, adhesions can be differentiated on the basis of location, into intra-abdominal or intrauterine.

Virtually, any transperitoneal operation can lead to the formation of intra-abdominal adhesions ranging from minimal scarring of serosal surface to firm agglutination of nearly all structures. The formation of adhesions following open gynaecological surgery has a considerable epidemiological and clinical impact. It has been reported that intra-abdominal adhesions occur in 60–90% of women who have undergone major gynaecological procedures (Monk et al., 1994; Metwally et al., 2006; Liakakos et al., 2001). Further, a recent study by Lower et al. (2000) conducted in Scotland reported that women undergoing an initial open surgery for gynaecological conditions had a 5% likelihood of being rehospitalized because of adhesions over the next 10 years and overall, adhesions may have contributed to rehospitalization in an additional 20% of patients.

Although many adhesions resulting from gynaecological surgery have little or no detrimental effect on patients, a considerable proportion of cases can lead to serious short- and long-term complications, including infertility (Becker et al., 1996; Risberg, 1997; Nagata et al., 1998; Milingos et al., 2000; Diamond and Freeman, 2001; Vrijland et al., 2003), pelvic pain (Duffy and diZerega, 1996; 1997; Risberg, 1997; Howard, 2000; Diamond and Freeman, 2001; Swank et al., 2003; Hammoud et al., 2004) and intestinal obstruction (Menzies, 1993; Al-Took et al., 1999; Ellis et al., 1999; Duron et al., 2000; Tulandi, 2001), resulting in a reduced quality of life (Menzies et al., 2006) often requiring readmission to hospital and additional more complicated surgical procedures (Diamond and El-Mowafy, 1998; Beck et al., 2000; Coleman et al., 2000; Van Der Krabben et al., 2000; Gutt et al., 2004) and indeed increased surgical costs (Ivarsson et al., 1997; Beck et al., 2000; Menzies et al., 2001).

Propensity to form adhesions has been hypothesized to be patient specific. Various individual factors such as nutritional status, disease states such as diabetes and the presence of concurrent infectious processes, which impair leukocyte and fibroblast function, potentially increase adhesion formation (Montz et al., 1986; Liakakos et al., 2001). It has also been shown that post-surgical adhesions increase with the patient’s age,
the number of previous laparotomies and the type and complexity of surgical procedures (De Cherney and diZerega, 1997).

When lysed, adhesions have a tremendous propensity to reform (Diamond and Freeman, 2001) over time with recurrence ranging from days to decades after surgery. Diamond remarked that adhesion reformation occurs post-operatively in 55–100% of patients, with a mean incidence of 85% (Diamond, 2000) irrespective of whether the adhesiolysis is performed via laparotomy or laparoscopy and independently of the character of the initial adhesion (Diamond et al., 1987). The latter concept contrasts with conclusions drawn by Parker et al. (2005), who found that thick lesions are significantly more likely to reform compared with thin or thin and thick adhesions and that adhesions involving the ovary are more likely to reform.

Since its first introduction in gynaecological surgery in 1986, laparoscopy with its minimal access to the peritoneal cavity has been claimed to be associated with reduced rates of adhesion formation (Hasson et al., 1992; Dubuisson et al., 1998; Schafer et al., 1998; Garrand et al., 1999; Miller, 2000; Kavic, 2002) and related complications, compared with traditional surgery (Tulandi et al., 1993). A few clinical and experimental studies as summarized in Table I have addressed the issue of comparing adhesion formation after laparoscopic and laparotomic surgery in gynaecology, with conclusive evidence suggesting a comparable or reduced adhesion formation rate in women who undergo laparoscopic procedures (Filmar et al., 1987; Luciano et al., 1989; Lundorff et al., 1991; Marana et al., 1994; Bulletti et al., 1996; Chen et al., 1998; Milingos et al., 2000; Mettler, 2003).

An epidemiologic study by Lower et al. (2004) reported on data from 24 046 patients undergoing laparoscopy or laparotomy for gynaecological conditions and partially contrasted with the results from the previous studies. Data from this study have supported the concept that laparoscopy is less adhesiogenic than laparotomy only with respect to laparoscopic tubal sterilization procedures, which represented a considerable proportion of laparoscopies (59%), and the vast majority of those categorized as having 'low-risk' (1 in 500) of directly adhesion-related readmission within the first year of surgery. However, for 'high-risk' (laparoscopic adhesiolysis and cyst drainage) and 'medium-risk' (other interventions not otherwise categorized) laparoscopies, which constituted >40% of gynaecological procedures, the risk of adhesion-related readmission has been shown to be considerable (1 in 80 and 1 in 70, respectively) and substantially higher than for the conventional approach (1 in 170) (Lower et al., 2004).

Any factor leading to a trauma of the endometrium may engender fibrous intrauterine bands at opposing walls of the uterus into conditions varying from minimal, marginal adhesions to complete obliteration of the cavity (Asherman, 1948; Asherman, 1950). The aetiology of intrauterine adhesions (IUAs) is multi-factorial, as it recognizes multiple predisposing and causal factors (Baggish Barbot and Valle, 1999) as summarized in Table II.

Approximately 90% of cases of IUAs are related to post-partum or post-abortion overzealous dilatation and curettage (Jensen and Stromme, 1972; March and Israel, 1976; Friedler et al., 1993; March, 1995; Dicker et al., 1996; Schenker, 1996; Pabuccu et al., 1997). Less frequently, IUAs are caused by postabortal (Louros et al., 1968) and puerperal sepsis (Polishuk et al., 1975), genital particulate infections such as tuberculous endometritis (Netter et al., 1956; Taylor et al., 1981; Schenker, 1996), pelvic irradiation and previous uterine surgery (Wu and Yeh, 2005). Furthermore, IUAs represent the major long-term complication of operative hysteroscopy (Fayez, 1986; Creinin and Chen, 1992; Kazer et al., 1992; Taskin et al., 2000). The frequency of post-operative IUAs development depends on the pathology initially treated (Taskin et al., 2000; Acunzo et al., 2003; Mukul and Linn, 2005) and is particularly high following resectoscopic myomectomy and metroplasty (Guida et al., 2004).

However, the actual prevalence of IUAs is difficult to determine for a number of reasons including the widely diverging number of therapeutic and illegal abortions in different parts of the world, the high incidence of genital tuberculosis in some countries, the degree of awareness of the physician and the criteria set in defining IUAs (Shenker and Margalioth, 1982; Al-Inany, 2001), and the progressively widespread use of hysteroscopic surgery (Hulka et al., 1995). Furthermore, it should be considered that some patients with IUAs remain asymptomatic, which makes their clinical and epidemiological assessment difficult.

IUAs may be asymptomatic, but their development may also result in hypomenorrhoea/amenorrhoea (Schenker, 1996), infertility (Kdous et al., 2003; Zikopoulos et al., 2004), recurrent Spontaneous abortion (Propst and Hill, 2000; Ventolini et al., 2004; Devi Wold et al., 2006), irregular periods with dysmenorrhoea and pelvic pain (Valle and Sciarra, 1988; Menzies, 1993), as well as obstetric morbidity, mainly related to abnormal

### Table I. Experimental, clinical and epidemiological studies comparing adhesion formation after laparoscopy versus laparotomy in gynaecological procedures

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Subjects (n)</th>
<th>Type of intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filmar et al.</td>
<td>1987</td>
<td>Rat (61)</td>
<td>Uterine injury</td>
<td></td>
</tr>
<tr>
<td>Luciano et al.</td>
<td>1989</td>
<td>Rabbit (20)</td>
<td>Standardized laser uterine + peritoneal injury</td>
<td></td>
</tr>
<tr>
<td>Marana et al.</td>
<td>1994</td>
<td>Rabbit (28)</td>
<td>Ovarian conservative surgery</td>
<td></td>
</tr>
<tr>
<td>Chen et al.</td>
<td>1998</td>
<td>Pig (50)</td>
<td>Pelvic and paraaortic lymphadenectomy</td>
<td></td>
</tr>
<tr>
<td>Lundorff et al.</td>
<td>1991</td>
<td>Human (73)</td>
<td>Surgery for tubal pregnancy</td>
<td></td>
</tr>
<tr>
<td>Bulletti et al.</td>
<td>1996</td>
<td>Human (32)</td>
<td>Myomectomy</td>
<td></td>
</tr>
<tr>
<td>Milingos et al.</td>
<td>2000</td>
<td>Human (21)</td>
<td>Periaxial adhesiolysis for infertility</td>
<td>L</td>
</tr>
<tr>
<td>Mettler</td>
<td>2003</td>
<td>Human (465)</td>
<td>Myomectomy</td>
<td></td>
</tr>
<tr>
<td>Lower et al.</td>
<td>2004</td>
<td>Human (24064)</td>
<td>Different gynaecological surgical procedures divided into:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Low-risk (Fallopian tube sterilization)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Medium-risk (therapeutic and diagnostic procedures not otherwise categorized)</td>
<td>L/ =</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High-risk (adhesiolysis and cyst drainage)</td>
<td>L</td>
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</table>

1. less adhesions in laparoscopic group; L. less adhesions in laparotomy group; =, same adhesions in both laparotomy and laparoscopy groups.
Table II. Predisposing and causative factors of intrauterine adhesion formation

<table>
<thead>
<tr>
<th>Predisposing factor</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual predisposition</td>
<td>There appears to be an individual constitutional factor causing certain patients to develop a severe form of IUA and others to be unaffected and undergoing the same procedure. This may also explain why some patients respond well to treatment but others experience recurrent adhesions and also explain why some develop adhesions in the absence of any attributable trauma (Shenker and Margalioth, 1982).</td>
</tr>
<tr>
<td>Gravid uterus</td>
<td>Gestational changes cause softening of the uterus, so that the traumatizing effect of an eventual curettage may result in the denudation of the basal layer of the endometrium with consequent loss of the regenerative mechanism. Curettage between the second and fourth week post-partum is more likely to cause adhesions than any other endometrial trauma (March, 1995; Shenker, 1996).</td>
</tr>
<tr>
<td>Infections</td>
<td>Its role is still controversial; no reports are available on a direct connection between clinical infections (fever, leukocytes, foul discharge) and IUA (Shenker, 1996).</td>
</tr>
<tr>
<td>Retained placenta remnants</td>
<td>They might facilitate the occurrence of infection and also promote increased fibroblastic activity and collagen formation before endometrial regeneration has taken place (Polishuk et al., 1975).</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>Women who nurse remain estrogen deficient for a prolonged period and thus the stimulus to endometrial regeneration is missing (Baggish Barbot and Valle, 1999).</td>
</tr>
<tr>
<td>Pelvic irradiation</td>
<td>Trauma of the endometrium (Baggish Barbot and Valle, 1999).</td>
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</tbody>
</table>

The heterogeneity of the available studies evaluating and comparing the different antiadhesive strategies has raised a number of controversial issues which neither allow for a meta-analysis nor allow for a definite conclusion to be formed on the effectiveness of such methods. The main controversial issues are outlined below.

(1) The interpretation of research related to adhesion formation and prevention is still essentially limited by the lack of a universal, acceptable and reproducible grading system to score adhesions (Monk et al., 1994; Gutt et al., 2004). Indeed, staging or classification of any medical or surgical disorder is the cornerstone to reach a univocal understanding, to facilitate communication among physicians and investigators, to give a true judgment on different modalities of treatment and to clarify the expected prognosis for every individual case. Various scoring systems have been suggested for the clinical staging of intrauterine adhesions including the classification initially proposed by Hulka (1982), the more acceptable classification conceived in 1985 by the American Fertility Society (1988) and the last, more comprehensive adhesion scoring system established in 1994 by the Adhesion Scoring Group (1994). Although the latter classification has been shown to produce a marked increase in reproducibility between surgeon pairs in scoring pelvic adhesions, at present, it has not been validated with clinical outcomes as none of these systems have ever been. This is mainly because all these classification methods warrant a second look to score adhesions, which would require an additional invasive surgical procedure; moreover, clinical outcomes risk reflecting the results of the second-look procedure rather than the status of the pelvis at the beginning of the procedure. However, recent studies have addressed this issue by suggesting ultrasound-based ‘soft markers’, transvaginal 3D ultrasonography or magnetic resonance imaging as non-invasive tools to be used to classify the pelvic adhesions (Seow et al., 2003; Mussack et al., 2005; Okaro et al., 2006). As for intraabdominal adhesions, many classifications of IUA have been suggested, mainly on the basis of hysteroscopic findings, including March et al. (1978), European Society Classification (Wamsteker and De Blok, 1995), the American Fertility Society Classification (American Fertility
Society, 1988), Valle and Sciarra (Valle and Sciarra, 1988), Donnez and Nisolle classification (Donnez and Nisolle, 1994) and, very recently, Nasr et al. (2000). As for intrabdominal adhesions, none of these classifications is universally accepted, thus making any comparison between the different studies impossible.

(2) The results of human and animal studies are not comparable not only because the extrapolation of the animal model to humans is uncertain, but also because the same rigorous evaluating system is not applied. Indeed, most data on the effectiveness of the various means of preventing post-operative intraperitoneal adhesions are derived from the experimental animal studies where adhesions are accurately assessed by means of necropsy examinations. The evaluation of adhesions in clinical studies is extremely difficult, as it requires a second-look laparoscopy or laparotomy and, even then, it is less accurate than a necropsy (Gutt et al., 2004).

(3) Controlled clinical trials of adhesion prevention in humans have been performed only on limited procedures (mostly infertility-related procedures) but not in more extensive gynaecological interventions (e.g. gynaecological oncology surgery). Therefore, results of those trials on adhesion prevention in humans can only apply to the limited clinical setting in which they have been performed and cannot be extended to another clinical setting, in the presence of different metabolic, haemostatic and infectious conditions (Monk et al., 1994). Thus, differences in the effectiveness of a certain adhesion prevention strategy may purely be due to the differences in the extent of surgery, rather than to the method in use.

(4) Results on the use of agents to prevent adhesions are also limited. Some of the agents used to prevent adhesions during reconstructive infertility procedures are frequently contraindicated during more extensive extirpative operations because of the increased dissection and tissue destruction associated with these procedures, as well as the medical circumstances under which they are performed (Monk et al., 1994).

**Strategies for adhesion prevention**

In search for effective methods for preventing adhesions, a variety of surgical techniques and agents have been advocated for the prevention of both intraperitoneal and intrauterine adhesion formation. The main approaches include adjusting surgical techniques, minimizing tissue trauma and applying pharmacological and/or barrier adjuvants, to decrease adhesion formation.

**Prevention of adhesion in laparoscopic gynaecological surgery**

**Surgical technique**

Since its first introduction into the armament of general as well as gynaecological surgical procedures, laparoscopy has been thought to have an advantage of reducing the formation of post-operative adhesions, as it seems to meet most of the well-known principles of atraumatic, gentle and bloodless surgery originally described as ‘microsurgical technique’ by Victor Gomel in his textbook (Gomel, 1983).

First of all, laparoscopy with its minimal access to the abdominal cavity reduces the amplitude of peritoneal injury, which seems to play a pivotal role in the pathophysiology of adhesion formation (Cheong et al., 2001; Liakakos et al., 2001; Rock, 1991) (Table III). Avoiding incisions through highly vascularized anatomical structures, e.g. muscle layers, and minimizing the extent of tissue trauma are the two confirmed basic principles for reducing post-operative adhesions (Moreno et al. 1996). Minimal access also prevents the abdominal cavity from exposure to air and foreign reactive materials. Therefore, drying of the peritoneal surfaces with loss of the phospholipid layer, which has been documented in more than 40 studies to favour adhesion formation, as well as inflammatory reaction and/or bacterial contamination of the peritoneal surface can be avoided (Drollette and Badaway, 1992). Reducing manipulation of structures distant from the operative site, e.g. avoiding the bowel packing, minimizes the mechanical damage of mesothelial cells and local ischaemia, thus reducing the formation of adhesions at locations distant from the operative site (Gutt et al., 2004) and speeding the return of peristalsis. This may further reduce fibrous adhesions and reduce permanent adhesion formation by mechanically separating the coalescent peritoneal surfaces (Menzies, 1993).

The laparoscopic magnified view enables a gentler handling and a more precise dissection of anatomical structures at the operative site, thus contributing to minimize the degree of tissue trauma. Moreover, recent findings seem to indicate that the laparoscopic environment may reduce post-operative adhesion formation by directly interfering with the fibrinolytic activity of peritoneum via the inhibition of plasminogen activator inhibitor 1 (PAI-1) released by mesothelial cells (Ziprin et al., 2003).

Such concepts contrast with conclusions drawn by Molinas et al. (2001) who have demonstrated that carbon dioxide (CO2) pneumoperitoneum during laparoscopic surgery may act as a cofactor in post-operative adhesion formation mostly by inducing peritoneal hypoxia through a compression of the capillary flow in the superficial peritoneal layers (Molinas and Konincks, 2000). Furthermore, it has been demonstrated that CO2 pneumoperitoneum induces respiratory acidosis that, if not corrected, leads to metabolic acidosis and metabolic hypoxia. This could be deleterious for the peritoneal cells and enhance the detrimental effect of the CO2 pneumoperitoneum-induced peritoneal ischaemic hypoxia (Molinas et al., 2004b).

This hypothesis of mesothelial hypoxia playing a key role in enhancing adhesion formation has been confirmed by a number of observations in animal models revealing increased adhesion formation with insufflation pressure and with duration of pneumoperitoneum (Molinas and Konincks, 2000; Molinas et al., 2001) and a decreased adhesion formation with the addition of no >3% of oxygen to CO2 pneumoperitoneum (Elkelani et al., 2004).

Further studies have shown that CO2 pneumoperitoneum enhances adhesion formation through an up-regulation of hypoxia inducible factors (Molinas et al., 2003b), plasminogen system (PAI-1) (Molinas et al., 2003c), members of the vascular endothelial growth factor family and placental growth factor (Molinas et al., 2003a, 2004a).

Furthermore, a role for reactive-oxygen species (ROS) in post-operative adhesion formation at laparoscopy has been suggested, since ROS is produced during the ischaemia-reperfusion process (insufflation of peritoneum = ischaemia; deflation of pneumoperitoneum = reperfusion) and the administration of ROS scavengers has been demonstrated to decrease adhesion formation (Binda et al., 2003).
Finally, high peritoneal temperature and dry gasse induced disc-\kern2em ication have been claimed as potential cofactors in adhesion formation. Indeed, hypothermia has been demonstrated to reduce the toxic effects of hypoxia and of the ischaemia-reperfusion process in mice (Binda et al., 2004); on the other hand, the use of humidified gases has been demonstrated to minimize adhesion formation induced by dessication. Thus, the concept of combining controlled intraperitoneal cooling with a rigorous prevention of dessication might be important for clinical adhesion prevention (Binda et al., 2006).

However, the relevance of the mouse data for human surgery still has to be proven. Moreover, whether any of those negative effects of pneumoperitoneum translates to a higher risk of adhesion compared with that of traditional surgery is yet to be demonstrated.

However, besides the potential advantages associated with the intrinsically minimally invasive laparoscopic technique, a further improvement in preventing adhesion formation in gynaecologic laparoscopy may be provided by the adherence to ‘good’ surgical techniques and use of newly developed instruments and surgical techniques (Table III).

Basic principles of microsurgery, liberal irrigation of the abdominal cavity and instillation of a large amount of Ringer’s lactate at the completion of the procedure should be followed (Tulandi, 1997).

Modern surgical devices are provided with both cutting and hemostatic activities, thus sparing the use of multiple ligatures, which also favour adhesions. The various laparoscopic instruments currently available have been claimed to be associated with different adhesion formation potentials as demonstrated in a recent animal study following a standardized uterine injury (Hirota et al., 2005). However, this concept contrasts with the previous findings by others reporting no major differences in adhesions following a mechanical or a bipolar injury and stressing, nor any differences due to the contribution of training and experience of the surgeon (expressed by the duration of surgery and perioperative bleeding) in post-operative adhesion formation (Ordonez et al., 1997).

Among the newly developed laparoscopic techniques, it is worth mentioning that temporary ovarian suspension is a technique recently proposed (Ouabha et al., 2004; Abuzeid et al., 2002) as a simple and effective method in preventing periovarian post-operative adhesions, especially in the case of surgery for advanced endometriosis. Less recent are the numerous adjusts in laparoscopic technique proposed to prevent adhesion formation in the case of myomectomy (Pellicano et al., 2003, 2005) or interventions for tubal pregnancy (Fujishita et al., 2004).

At present, virtually, every gynaecologist performing pelvic surgery by laparoscopic techniques believes that this results in fewer post-operative adhesions than similar procedures performed at laparotomy. Although some animal data and far fewer human studies, as discussed above, seem to confirm this belief, until well-designed, randomized, controlled, clinical trials confirm this assumption, the concepts of ‘microsurgical techniques’ and ‘minimal access’ surgery will remain beneficial in theory alone (Johns, 2001).
Pharmacological adjuvants

A wide variety of pharmacological adjuvants, including steroidal and non-steroidal anti-inflammatory agents, antihistamines, progestosterone, gonadotrophin-releasing hormone (GnRHa) agonists, fibrinolytics and anticoagulants have been tested to prevent post-operative adhesion formation following open abdominal surgery without any clearly demonstrated advantage (Watson et al., 2000; Liakakos et al., 2001).

On the contrary, only one study evaluating pharmacological adjuvants to prevent adhesion formation in laparoscopic procedures has been found in the English language (Fayez and Schneider, 1987) (Table IV).

Anti-inflammatory agents. Agents showing anti-inflammatory properties, including anti-inflammatory drugs (both steroidal and non-steroidal), antihistamines, progestogens, GnRH agonists and calcium-channel blockers have been advocated for preventing adhesion formation on the basis of encouraging data derived from animal studies (Holtz, 1984; Jansen, 1991; diZerega, 1994).

Anti-inflammatory non-steroidal agents have been used with success in preventing adhesion formation in several animal studies (Cofer et al., 1994; Golan et al., 1995; Tayyar and Basbug, 1999; Guvenal et al., 2001). Steroids and antihistamines have been used in both experimental (Hockel et al., 1987) and clinical studies in the setting of either laparotomy (Rock et al., 1984; Jansen, 1985; Querleu et al., 1989; Jansen, 1990a, b) or laparoscopic procedures (Fayez and Schneider, 1987); indeed, it was expected that they would be effective in preventing adhesions by exerting both anti-inflammatory and anti-fibrinolytic actions. However, there is no significant evidence from any published study to recommend their use in humans, and several side effects still have to be ascertained (Watson et al., 2000; Metwally et al., 2006).

Progestosterone has been investigated for reduction of post-operative adhesions after the initial observation that adhesions were reduced after ovarian wedge resection if that ovary was containing an active corpus luteum at the time of operation (Eddy et al., 1980). Although, both the experimental (Mori et al., 1977; Clemens et al., 1979) and animal studies (Nakagawa et al., 1979) have elicited the anti-inflammatory and immunosuppressive properties of progesterone and validated its effectiveness in preventing adhesions (Maurer and Bonaventura, 1983; Montanino-Oliva et al., 1996; Baysal, 2001), other studies have either failed to confirm these findings (Beauchamp et al., 1984) or noted an increase in adhesion formation when medroxyprogesterone acetate was used intramuscularly or intraperitoneally (Holtz et al., 1983; Blauer and Collins, 1988). However, data pertaining to the role of progesterone in preventing post-operative adhesion formation reported exclusively on patients treated by traditional surgery, and no studies performed in the setting of laparoscopic procedures have been found in the English language. At present, the use of progesterone in preventing adhesion development in clinical practice is also not recommended.

Combined pre-operative and post-operative treatment with GnRH agonists has been shown to decrease adhesion formation and reformation in both animal models (Wright and Sharpe-Timms, 1995) and clinical trials (Imai et al., 2003). Among the various direct and indirect actions through which GnRH agonists might modulate adhesion formation, the interference with fibrinolytic processes seems to be predominant. On the basis of the data available, adhesion prevention seems to be at its best when pre- (2–3 months) and post-operative (2–3 months) GnRH agonists treatment is administered (Imai et al., 2003; Schindler, 2004). At present, no studies evaluating the role of GnRH agonists in preventing adhesion following laparoscopic gynaecological procedures are available in the literature.

In some animal models, calcium-channel blockers whether subcutaneously or intraperitoneally administered have been shown to exert a number of anti-inflammatory actions leading to a reduction in both de novo and secondary adhesion formation (Steinleitner et al., 1988, 1989, 1990). However, these findings were not confirmed in other animal studies and thus have never been followed by studies in humans.

Fibrinolytic agents. An imbalance between fibrin-forming (coagulation) and fibrin-dissolving (fibrinolytic) activities in the peritoneum has been hypothesized as one of the major pathogenetic factors in adhesion development in animals (Holmdahl, 1997; diZerega and Campeau, 2001; Cheong et al., 2001). A recent prospective study in humans by Hellebrekers et al. (2005) seems to add further weight to the hypothesis that this applies to humans also. Fibrinolytic agents have been suggested in preventing adhesions, as they act directly by reducing the fibrinous mass and indirectly by stimulating plasminogen activator (PA) activity. Thrombolytic agents including plasmin preparations (plasmin, actase and fibrinolyxin) and plasmin activators (streptokinase, urokinase and recombinant human tissue PA) have been found to be effective in preventing adhesion formation in the greater part of the reviewed animal and clinical studies (Hellebrekers et al., 2000). However, the current use of fibrinolytic agents in humans awaits further evaluation of their safety and side effects. Moreover, studies pertaining to the role of fibrinolytic agents on the prevention of adhesion after gynaecological laparoscopic surgery are still missing.

Anticoagulants. Heparin is the most widely investigated anticoagulant used for prevention of adhesions. Its mechanism of action may be mediated by an interaction with antithrombin III in the cladding cascade or by a direct stimulation of the activity of PAs. Animal studies where heparin was administered by different routes either alone or in combination with peritoneal irrigants, carboxymethylcellulose instillates or mechanical barriers (Diamond et al., 1991a, b; Tayyar et al., 1993), resulted in conflicting reports demonstrating its efficacy in reducing adhesion formation and reformation. However, the efficacy of heparin in reducing adhesion formation whether administered alone (Jansen, 1988) or in combination with Interceed TC7 barrier (Reid et al., 1997) was not able to be demonstrated in the two clinical trials available in the literature.

Also, heparin was found to have no therapeutic advantage over Ringer’s lactated solution in the prevention of post-operative pelvic adhesion, in the paper reporting on patients undergoing laparoscopic surgery for different gynaecological conditions (Fayez and Schneider, 1987).

Antibiotics. The rationale behind the use of antibiotics is prophylaxis against infection and hence the inflammatory response that triggers the adhesion formation. Systemic broad-spectrum antibiotics, particularly cephalosporins, were widely used in the
### Table IV. Pharmacological agents to prevent and/or decrease adhesion formation

<table>
<thead>
<tr>
<th>Pharmacological agent</th>
<th>Mechanism(s) of action</th>
<th>Experimental studies</th>
<th>Animal studies</th>
<th>Human studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Laparotomy</td>
<td>Laparoscopy</td>
<td>Laparotomy</td>
</tr>
<tr>
<td><strong>Anti-inflammatory agents</strong></td>
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<tr>
<td>Calcium channel blockers</td>
<td>Anti-inflammatory actions</td>
<td>–</td>
<td>–</td>
<td>Steinleitner et al. (1988, 1989, 1990)</td>
</tr>
<tr>
<td>Plasmin preparations</td>
<td>Prophylaxis against infections and hence the inflammatory response that triggers the adhesion formation</td>
<td>–</td>
<td>–</td>
<td>Gutmann and Diamond (1992), Gutmann et al. (1995)</td>
</tr>
<tr>
<td>Plasmin activators</td>
<td>Anti-inflammatory actions</td>
<td>–</td>
<td>–</td>
<td>Steinleitner et al. (1988, 1989, 1990)</td>
</tr>
</tbody>
</table>
past. At present, there is insufficient published data from animal or human studies supporting this practice. Indeed, antibiotics in intraperitoneal irrigation solutions have been demonstrated to increase peritoneal adhesion formation in rat model and thus are not recommended as a single agent for adhesion prevention (Gutmann and Diamond, 1992; Gutmann et al., 1995).

**Barrier adjuvants**
Mechanical separation of peritoneal surfaces of the pelvic organs during the early days of the healing process post-operatively is a practical way to prevent post-operative adhesions. This separation may be accomplished by intraabdominal instillates and solid barriers (endogenous tissue or exogenous material) as summarized in Table V. The ideal barrier should be noninflammatory, nonimmunogenic, persist during the remesothelialization, stay in place without suture, remain active in the presence of blood and be completely biodegradable.

**Solid barriers**
*Omental grafts.* The original ‘barriers’ consisted of peritoneal and omental grafts placed over traumatized surfaces and sewn in place. This practice places a layer of dead necrotic tissue on top of traumatized peritoneal surfaces, thus providing an abundant supply of substrate for adhesion formation. Subsequent animal studies have demonstrated that placing devascularized tissue over damaged peritoneal surfaces increases rather than decreases adhesion formation. Although no human randomized trials dealing with gynaecological surgery have been performed, the animal data are convincing enough that this practice has been abandoned (Johns, 2001).

*Oxidized regenerated cellulose. Oxidize regenerated cellulose (ORC) (Interceed®; Johnson & Johnson Medical Inc.) is the most widely used adhesion-reducing substance and has been shown in both animal (Marana et al., 1997) and human studies (Sekiba, 1992; Azziz, 1993; Franklin, 1995; Mais et al., 1995a; Wallwiener et al., 1998) to reduce adhesion formation by its transformation into a gelatinous mass covering the damaged peritoneum and forming a barrier physically separating adjacent raw peritoneal surfaces. The use of ORC was associated with a reduced incidence of both de novo (Mais et al., 1995b) and reformed adhesions as diagnosed at the second-look laparoscopy. In the first study, Mais et al. (1995b) reported a significant reduction of de novo adhesion formation in premenopausal women undergoing laparoscopic myomectomy with the application of ORC on the uterine incisions and sutures, in comparison with those undergoing the same surgery but without any specific antiadhesive strategy. In the second study (Mais et al., 1995a), reporting on 32 premenopausal women affected by severe endometriosis and complete posterior cul-de-sac-obliteration undergoing laparoscopic surgery with or without specific treatment for adhesion prevention, the authors demonstrated that the application of ORC at the end of the surgery to cover the deperitonealized areas and ovaries was effective in significantly reduced adhesion reformation.

It is essential that complete hemostasis is achieved before ORC is placed on the peritoneal surface, as the presence of intraperitoneal blood negates any beneficial effect. In fact, small amounts of bleeding result in blood permeating the weave of the material and in fibroblasts growing along the strands of clotted blood with subsequent collagen deposition and vascular proliferation (De Cherney and diZerega, 1997). Moreover, it has been suggested (Grow et al., 1994) that migration of the barrier may occur after application, thus reducing its effectiveness.

ORC has been shown to act in synergy with heparin (Wiseman et al., 1992). In animal models, the application of heparin-treated ORC adhesion barriers significantly reduced adhesion score (Diamond et al., 1991a). Although adhesion reduction was also observed in human studies, it did not reach statistical significance when compared with untreated ORC (Reid et al., 1997).

*Expanded polytetrafluoroethylene. Expanded polytetrafluoroethylene non-absorbable barrier (Gore-Tex Surgical Membrane®,
WL Gore & Associates, Inc., Newark) has also undergone evaluation in a randomized multicentre controlled trial (Haney et al., 1995). This product must be sewn in place and is usually removed during a second surgical procedure. In patients undergoing gynaecological surgery by laparotomy for adhesions or myoma, Gore-Tex Surgical Membrane was shown to decrease the severity, extent and incidence of adhesions in treated areas. Its usefulness is limited by the nature of the product: it must be sutured in place and, in most cases, should be removed at a subsequent surgery. It is very difficult to apply at laparoscopy.

**Intraabdominal instillates**

**Crystalloids.** The instillation of such large volume isotonic solutions (normal saline, Ringer’s lactate, etc.) into the peritoneal cavity at the end of surgery to produce a ‘hydroflatation’ effect has represented the most popular and economic agent used for adhesion prevention in gynaecological surgery. However, a meta-analysis of clinical trials has shown that crystallloid solutions do not reduce the formation of post-surgical adhesions whether in laparoscopy or in laparotomy (Wiseman et al., 1998). This seems to be due to the rapid absorption rate of the peritoneum (30–60 ml h), which ensures a nearly complete assimilation of the fluid into the vascular system within 24–48 h, far too short time to influence adhesion formation.

**Icodextrin.** Icodextrin (ADEPT, Baxter, USA) is an α-1,4 glucose polymer of high molecular weight, which is rapidly metabolized to glucose by the α-amylase in the systemic circulation, but is adsorbed only slowly from the peritoneal cavity. The 4% solution of icodextrin, having a longer peritoneal residence time (≥4 days) than crystallloid solutions (Hosie et al., 2001), has the potential to significantly reduce post-surgical adhesion formation by means of a prolonged hydroflatation.

Preclinical studies with 4% icodextrin in the rabbit double uterine horn model demonstrated that in addition to the significant benefits of post-operative instillation, de novo formation of adhesions was significantly reduced by frequent intra-operative irrigation (Verco et al., 2000).

In a randomized, controlled, pilot study, diZerega et al. (2002) showed that lavage plus instillation with 4% icodextrin was well tolerated and reduced incidence, extent and severity of adhesion formation and reformation following laparoscopic adnexal surgery even if the group sizes were not powered for statistical significance. In a recent randomized, double-blind trial Brown and colleagues (Brown et al., 2007) confirmed the previous results by demonstrating 4% icodextrin to be effective and safe in reducing adhesions in patients undergoing gynaecological laparoscopy involving adhesolysis.

Currently, there is insufficient evidence to recommend the use of such agent in the adhesion prevention in laparoscopic gynaecological surgery (M CWally et al., 2006).

**Hyaluronic acid.** Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan and a major component of the extracellular matrix, including connective tissue, skin, cartilage and vitreous and synovial fluids. This polymer is biocompatible, nonimmunogenic, non-toxic and naturally bioabsorbable. Intraperitoneal instillation coats serosal surface, minimizes serosal desiccation and reduces adhesion formation (Burns et al., 1996). However, its use after tissue injury is ineffective.

Cross-linking HA with ferric ion (FeHA) increases the viscosity and half-life. Johns et al. (2001) in a large multicentre randomized study showed that Intergel (Johnsson & Johnson Gyneecare Unit, NJ, USA), the first marketed derivative of FeHA, was effective in reducing the extension and the severity of post-operative adhesions in comparison to lactated Ringer’s solution in patients undergoing peritoneal cavity surgery by laparotomy with a planned second-look laparoscopy. Likewise, in three other randomized trials (Hill-West et al., 1995; Thornton et al., 1998; Lundorff et al., 2001), ferric hyaluronate gel was demonstrated to be safe and highly efficacious in reducing the number, severity and extent of adhesions throughout the abdomen following pelvic laparotomic surgery. No studies evaluating the role of Intergel in preventing adhesion following laparoscopic gynaecological procedures have been found in the international literature. Since 2003, the product has been removed from the market due to the reported pelvic pain and allergic reactions.

Auto-cross linked HA gels (ACP gel, Hyalobarrier Gel, Baxter, Italy) (De Iaco et al., 1998, 2001) are particularly suitable for preventing adhesion formation because of their higher adhesivity and prolonged residence time on the injured surface than unmodified HA (Mensitieri et al., 1996). In a prospective, randomized, controlled study, Pellicano et al. (2003) showed that in 36 patients treated by laparoscopic myomectomy and application of the ACP gel, the rate of subjects who developed post-operative adhesions was significantly lower in comparison with patients treated by laparoscopic myomectomy alone (27.8% versus 77.8%). Moreover, the rate of post-surgical adhesions was also significantly dependent on the types of laparoscopic sutures that were used to close uterine defects, in both treated patients and controls. Further, the authors demonstrated that the application of ACP as an antiadhesive barrier in infertile patients undergoing laparoscopic myomectomy is associated with the increased pregnancy rates than laparoscopic myomectomy alone (Pellicano et al., 2005). The favourable safety profile and the efficacious antiadhesive action of this adjunct following laparoscopic myomectomy have been recently confirmed in a blinded, controlled, randomized, multicentre study by Mais et al., 2006).

**Solution of HA.** Seprocoat coating solution (Genzyme, Cambridge, MA, USA), a liquid composed of 0.4% sodium hyaluronate (hyaluronic acid) in phosphate buffered saline, is applied intraoperatively, prior to dissection, to protect peritoneal surfaces from indirect surgical trauma or post-operatively to separate surfaces after they are traumatized. In animal models, this solution reduced serosal damage, inflammation and post-surgical adhesions (Burns et al., 1995; Ustun et al., 2000). In humans, preliminary results were promising (Keckstein et al., 1996) and have been confirmed in a multicentre randomized trial where intraperitoneal Seprocoat instillate was safe and significantly more effective than placebo in reducing the incidence, extent and severity of de novo adhesions to multiple sites indirectly traumatized by gynaecologic laparotomic surgery (Diamond, 1998). No studies evaluating the role of Seprocoat in preventing adhesion following laparoscopic gynaecological procedures are available in the literature.

Currently, the insufficient evidence of clinical effectiveness has not lead to continuous development and promotion of this product.
Viscoelastic gel. Oxiplex/AP Gel (FzioMed, San Louis Obispo, CA, USA) is a viscoelastic gel composed of polyethylene oxide and carboxymethylcellulose stabilized by calcium chloride specifically formulated for laparoscopic application, with tissue adherence and persistence sufficient to prevent adhesion formation. Following the encouraging results of preclinical studies (Berg et al., 2003; Lundorf et al., 2005) published the results of a randomized, third-party blinded, multicentre European trial showing that viscoelastic gel did significantly reduce adnexal adhesions in patients undergoing gynaecological laparoscopic surgery. Simultaneously, Young et al. (2005) performed a prospective, multicentre, double-blind, randomized study evaluating the efficacy of Oxiplex/AP Gel and reported that viscoelastic gel was safe, easy to use with laparoscopy and produced a reduction in the increase of adnexal adhesion scores.

Hydrogel. SprayGel (Confluent Surgical, Waltham, MA, USA) consists of two synthetic liquid precursors that, when mixed, rapidly cross-link to form a solid, flexible, absorbable hydrogel. The solid polymer acts as an adhesion barrier and it can be easily applied by laparoscopy (Dunn et al., 2001; Ferland et al., 2001). The currently available evidence does not support the use of SprayGel either in decreasing the extent of adhesion or in reducing the proportion of women with adhesions (Johns et al., 2003; Mettler et al., 2004).

Fibrin sealant. Fibrin sealant is a two-component substance that can be applied as a liquid solution to the tissue. The mixture of the two substances becomes a highly polymerized solid fibrin film. In several animal studies, the results have been inconsistent. However, Takeuchi et al. (2005) in a recent prospective, randomized, controlled study reported that fibrin gel (Beriplast, ZLB Behring, USA) was able to significantly reduce the frequency of post-operative uterine adhesions after laparoscopic myomectomy, with no significant difference in the incidence of de novo adnexal adhesions. At present, Beriplast is not available in all countries and the licenced indications may vary from country to country.

Prevention of IUA in hysteroscopic surgery

Surgical technique
As for laparoscopy, the adherence to an appropriate hysteroscopic surgical technique may minimize the risk of post-operative IUA.

General recommendations include avoiding trauma of healthy endometrium and myometrium surrounding the lesions to be removed, reducing the usage of electrosurgery whenever possible (Chen et al., 1997) especially during the removal of myomas with extensive intramural involvement (Mazzon, 1995) and avoiding forced cervical manipulation.

Data comparing monopolar and bipolar electrosurgery on post-operative IUA formation are still lacking in the literature.

Early second-look hysteroscopy
An early second-look hysteroscopy after any hysteroscopy surgery has been advocated as an effective preventive and therapeutic strategy (Wheeler and Taskin, 1993). Indeed, although IUAs are recognized, they are likely to be ‘mild’ and they can be easily dissected by hysteroscope sheath alone or by microscissors. However, the relevance of removing ‘mild’ intracavitary adhesions has not yet been proven. Furthermore, diagnostic hysteroscopy has been demonstrated to be an ‘unforced intrauterine intervention’ with no increased risk of IUA development (Fedorkow et al., 1991).

Antibiotic administration
Antibiotic administration before, during and after hysteroscopic surgery to avoid infections and therefore to prevent post-operative IUA is not consistently recommended (Schenker, 1996).

Pre-operative hormonal endometrial suppression
GnRH analogues and danazol are widely administered before some major hysteroscopic procedures (e.g. transcervical resection of endometrium, myomectomy and metroplasty) to provide technically optimal conditions for the surgery (by suppressing the endometrium and by decreasing vascularity and oedema), as well as to minimize perioperative complications (perforation, fluid overload and bleeding). The role of endometrial suppression before resectoscopic surgery on the frequency of post-operative IUA has been questioned. Taskin et al. (2000) recently demonstrated in the only randomized study available in the English language that the frequency of post-operative IUA was dependent on the pathology initially treated with no difference between placebo- and danazol-treated (200 mg twice/day) groups. However, the small sample size does not allow for a definite conclusion to be drawn (Taskin et al., 2000).

Data pertaining to the role of pre-operative GnRH analogues on the development and/or re-development of IUA after hysteroscopic surgery were not found in the English language.

Post-operative hormonal treatment
The post-operative administration of conjugated oestrogen (dose: 1.25–5 mg daily) for 30–60 consecutive days and progestin therapy in a cyclic regimen seem to stimulate the endometrium so that the scarred surfaces are re-epithelialized (Chen et al., 1997; Farhi et al., 1993). However, the efficacy of this method needs to be validated by large randomized studies. The insertion of a levonorgestrel-releasing intrauterine device (IUD) might represent another promising tool to prevent IUA adhesions, but studies addressing this issue are still missing.

Barrier methods
The maintenance of the freshly separated uterine cavity after any uterine forced intervention is an essential prerequisite for prevention of subsequent adhesion formation, whereas rapid endometrial re-growth might be enhanced by oestrogen and progestogens cyclic administration (Shenker and Margalioth, 1982). Few studies evaluating the efficacy of barrier methods for the prevention of IUA after hysteroscopic surgery are available at present.

Intrauterine device.
For several years, the placement of an IUD in the uterine cavity for 3 months has been considered the standard method of maintaining the uterine cavity after uterine forced intervention (Comninos and Zourlas, 1969; Massouras, 1974; Jewelewicz et al., 1976; Sugimoto, 1978; Corson, 1992; Shenker and Margalioth, 1982; Valle and Sciarra, 1988). However the specific type to be used for this purpose remains a controversial issue. The copper-bearing IUDs and the prostasert intrauterine system (IUS) seem to have a too small surface area to prevent adhesion formation.
reformation, whereas those containing copper might induce an excessive inflammatory reaction. Actually, the loop-IUS seems to represent the best to use as it keeps the raw dissected surfaces separated during the initial healing phase, reducing the chance of re-adherence (Shaffer, 1986). Despite good results, this method has been associated with several complications such as infections, uterine perforation, misplacement of the device and IUA recurrence (Otubu and Olarewoju, 1989; Ogedegbe et al., 1991). Prophylactic antibiotics are recommended to minimize the risk of infection (Chen et al., 1997).

No large randomized controlled studies evaluating the efficacy of this device in specifically preventing IUA after hysteroscopic surgery have been found in the international literature.

Foley catheter balloon. Reportedly, an inflated pediatric Foley catheter balloon inserted into the uterine cavity for several days retains separation of the uterine walls with fewer complications in comparison with IUDs (Wallach, 1979; Ozumba and Ezegorui, 2002; Doody and Carr, 1990; Speroff et al., 1994; Orhue et al., 2003; Shenker and Margalioth, 1982). Its use is however limited because of the need for hospitalization during the duration of treatment, pain and the shortness of the treatment period which, in itself, is an obstacle in ensuring definitive results in preventing IUA (Schenker, 1996).

In a population of 40 women with recurrent pregnancy loss or infertility resulting from IUA, it has been demonstrated that hysteroscopic adhesiolysis followed by the introduction of an 8F Foley catheter was not only safe but also effective in the restoration of normal menstrual pattern and fertility (Pabuccu et al., 1997).

Large randomized studies evaluating the efficacy of this device in specifically preventing IUA after hysteroscopic surgery are lacking.

Auto-cross-linked HA gel. In 2003, Acunzo et al. (2003) described the introduction of APC gel into the uterine cavity at the end of the hysteroscopic surgery through the out-flow channel of the resectoscope, whereas the surgeon progressively limits the entering of the distension medium through the in-flow channel. The procedure is considered complete when, under hysteroscopic view, the gel seems to have replaced all the liquid medium and the cavity appears completely filled by the gel from tubal ostia to internal uterine orifice (Fig. 1). Its high viscosity and adhesiveness make it easier to introduce the gel into the uterine cavity and ultrasound scans have confirmed that APC gel remains in situ for at least 72 h (Fig. 2A and B).

In this randomized study, Acunzo and co-workers demonstrated that the intrauterine application of APC gel following hysteroscopic adhesiolysis significantly reduces the reformation of post-operative IUA. Furthermore, APC gel was associated with a significant reduction of the severity of IUA. In a further randomized controlled study, Guida et al. (2004) showed that APC also significantly reduces the incidence and severity of de novo formation of IUA after resectoscopic removal of myomas, polyps and septa.

![Figure 1. Hysteroscopic view of the uterine cavity distended by the auto-cross linked hyaluronic acid (ACP) gel applied at the end of the hysteroscopic procedure through the out-flow channel of the resectoscope, whereas the surgeon progressively limits the entering of the distension medium through the in-flow channel.](http://humupd.oxfordjournals.org/)

![Figure 2. Ultrasonographic image of APC gel remaining in the uterine cavity after 24 h (A) and 72 h (B).](http://humupd.oxfordjournals.org/)
The real effect of the prevention of IUAs on long-term reproductive outcome is not clear but will emerge from ongoing works. **HA and carboxymethylcellulose barrier.** Seaprafilm (Genzyme Corporation, Cambridge, MA, USA) is a bioresorbable membrane of chemically modified HA and carboxymethylcellulose, which has been shown to be effective in reducing adhesion formation after suction curettage for incomplete and missed abortion (Tsapanos et al., 2002). It has never been tested for preventing IUAs after hysteroscopic surgery.

**Conclusions**

Although minimally invasive endoscopic approach has been shown to be less adhesiogenic than traditional surgery, at least with regard to selected procedures, it does not however totally eliminate the problem. Consequently, many attempts have been made to further reduce adhesion formation following endoscopic procedures and many surgical techniques; pharmacological agents and mechanical barriers have been advocated to address this issue.

The present review clearly indicates that there is still no single modality proven to be unequivocally effective in preventing post-operative adhesion formation either for laparoscopic or for hysteroscopic use. Furthermore, the available adhesion-reducing substances are rather expensive. Much work needs to be done to enhance this adjuvant therapy, since excellent surgical technique alone seems insufficient. Hopefully, the increasing understanding of the pathophysiology of peritoneal healing will provide the rational basis for the development of further specific interventions at critical points along the adhesion formation cascade. The future emphasis will probably be on a multimodality therapy, including the use of pharmacological adjuvants in conjunction with a barrier material tailored to the specific operative procedure and a precise surgical technique.

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