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Prevention of adhesions in gynaecological endoscopy

C.Nappi[1], A.Di Spiezio Sardo[1,2], E.Greco[1], M.Guida[1], S.Bettocchi[3] and G.Bifulco[1]

[1]Department of Gynaecology and Obstetrics, and Pathophysiology of Human Reproduction, University of Naples 'Federico II', Via Pansini 5, Naples, Italy and [3]Department of General and Specialistic Surgical Sciences, Section of Obstetrics and Gynaecology, University of Bari, Italy

[2]To whom Correspondence should be addressed at: Department of Gynaecology and Obstetrics, and Pathophysiology of Human Reproduction, University of Naples 'Federico II', Via Pansini 5, Naples, Italy. Fax: +39-0817462905; E-mail: cdispie@tin.it

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 intraabdominal 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 intraabdominal 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-Mowafi, 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 IUA 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 tubercolous 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 IUA 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 IUA 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 IUA (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 IUA remain asymptomatic, which makes their clinical and epidemiological assessment difficult.

IUA 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

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

l, 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

	Mechanism of action
Predisposing factor	
Individual predisposition	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).
Gravid uterus	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; Schenker, 1996).
Infections	Its role is still controversial; no reports are available on a direct connection between clinical infections (fever, leukocytes, foul discharge) and IUA (Schenker, 1996).
Retained placenta remnants	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).
Breast-feeding	Women who nurse remain estrogen deficient for a prolonged period and thus the stimulus to endometrial regeneration is missing (Baggish Barbot and Valle, 1999).
Causative factors	
Forced intrauterine intervention Post-partum or post-abortion dilatation and curettage Operative hysteroscopy Uterine surgery (e.g. caesarean section, myomectomy)	Trauma of the endometrium (Baggish Barbot and Valle, 1999).
Pelvic irradiation	Trauma of the endometrium (Baggish Barbot and Valle, 1999).
Genital particulate infections (tubercolous endometritis, puerperal and post-abortion sepsis)	Chronic inflammation of the endometrium (Baggish Barbot and Valle, 1999).

placentation (Musset *et al.*, 1960; Klein and Garcia, 1973; Jewelewicz *et al.*, 1976; Cook and Seman, 1981; Shenker and Margalioth, 1982; Valle and Sciarra 1988; Magos *et al.*, 1991; Whitelaw *et al.*, 1992; Wood and Rogers, 1993; Ismail *et al.*, 1998; Pugh *et al.*, 2000; Taskin *et al.*, 2002; Mukul and Linn, 2005).

The purpose of the present review is to provide gynaecologists with special interest in endoscopy a brief analysis of the open issues regarding adhesion development and a precise survey of the various measures of preventing adhesions in gynaecological laparoscopic and hysteroscopic surgery. This review includes medical papers published in the English language on adhesion prevention in gynaecological endoscopy since 1986 and identified through a MEDLINE search using combinations of medical subject heading terms: *adhesion, surgical technique, adhesion barriers, anti-adhesion liquids, pharmacological agents, gynaecological surgery, laparoscopy, hysteroscopy*. All pertinent articles were retrieved and reports were then selected through systematic review of all references. In addition, books and monographs on adhesion formation and prevention in gynaecological surgery were consulted.

Open issues in evaluating adhesion formation

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 intraperitoneal 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', transavaginal 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 gynaecolgical 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 fibrinous 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 (CO_2) 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 Koninckx, 2000). Furthermore, it has been demonstrated that CO_2 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 CO_2 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 Koninckx, 2000; Molinas *et al.*, 2001) and a decreased adhesion formation with the addition of no $>3\%$ of oxygen to CO_2 pneumoperitoneum (Elkelani *et al.*, 2004).

Further studies have shown that CO_2 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).

Table III. Potential advantages of laparoscopic approach in reducing adhesion formation in gynaecological surgery

Potential advantages associated with the intrinsically minimally invasive laparoscopic approach	
Minimal access to the abdominal cavity	
Reduced amplitude of peritoneal injury	Rock (1991), Cheong *et al.* (2001), Liakakos *et al.* (2001)
Avoidance of incisions through highly vascularized anatomical structures	Moreno *et al.* (1996)
Minimized extent of tissue trauma	Moreno *et al.* (1996)
Prevention of the abdominal cavity from exposure to air and foreign reactive materials	Drollette and Badaway (1992)
Reduced manipulation of structures distant from the operative site	
Reduced mechanical damage of mesothelial cells and local ischaemia	Menzies (1993), Gutt *et al.* (2004)
Reduced bowel packing with consequent speeding of the return of peristalsis and mechanical separation of the coalescent peritoneal surfaces	
Gentler handling and precise dissection of anatomical structures provided by the laparoscopic magnified view	
Minimized degree of tissue trauma	Liakakos *et al.* (2001)
Positive interference exerted by the laparoscopic environment on the peritoneal fibrinolytic activity	
Inhibition of plasminogen activator inhibitor 1 released by mesothelial cells	Ziprin *et al.* (2003)
Potential advantages associated with the adherence to 'good' surgical technique	
Adherence to the basic principles of microsurgery	Tulandi (1997)
Liberal irrigation of the abdominal cavity and instillation of a large amount of Ringer's lactate at the completion of the procedure	Tulandi (1997)
Potential advantages associated with the use of newly developed instruments	
Electrothermal bipolar vessel sealer is associated with a reduced post-operative adhesion formation in comparison with ultrasonically activated scalpel and monopolar electrocautery	Hirota *et al.* (2005)
Potential advantages associated with the use of new surgical techniques	
Temporary ovarian suspension to prevent peri-ovarian post-operative adhesions	Abuzeid *et al.* (2002), Ouahba *et al.* (2004)
In case of laparoscopic myomectomy, subserous sutures are associated with a significantly lower adhesion rate and higher pregnancy rate in comparison with interrupted 'figure 8' sutures	Pellicano *et al.* (2003, 2005)
The suture of tube at linear salpingotomy does not offer significant advantage over the non-suturing technique in terms of reduction of postsurgical tubal adhesions	Fujishita *et al.* (2004)

Finally, high peritoneal temperature and dry gasse induced dessication 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 humified 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 (Ouahba *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; Pellicano *et al.*, 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 dicussed 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, progesterone, 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 laparotomic (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).

Progesterone 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- (2–3months) 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 fibrinolysin) 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 clouding 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

Pharmacological agent	Mechanism(s) of action	Experimental studies		Animal studies		Human studies	
		Laparotomy	Laparoscopy	Laparotomy	Laparoscopy	Laparotomy	Laparoscopy
Anti-inflammatory agents Non-steroidal anti-inflammatory drugs	Anti-inflammatory action	–	–	Cofer *et al.* (1994), Golan *et al.* (1995).Tayyar and Basbug, (1999), Guvenal *et al.* (2001)	–	–	–
Steroidal agents	Anti-inflammatory plus anti-fibrinolytic actions	Hockel *et al.* (1987)	–	–	–	Rock *et al.* (1984), Jansen (1985, 1990a, b), Querleu *et al.* (1989)	Fayez and Schneider (1987)
Anti-histamines	Anti-inflammatory plus anti-fibrinolytic actions	Hockel *et al.* (1987)	–	–	–	Rock *et al.* (1984), Jansen, (1985, 1990a, b), Querleu *et al.* (1989)	Fayez and Schneider (1987)
Progestogens	Anti-inflammatory plus immunosuppressive proprieties	Mori *et al.* (1977), Clemens *et al.* (1979)	–	Nakagawa *et al.* (1979)	–	Eddy *et al.* (1980), Maurer and Bonaventura (1983), Holtz *et al.* (1983), Blauer and Collins (1988), Beauchamp *et al.* (1984), Montanino-Oliva *et al.* (1996)	–
GnRH agonists	(i) Induction of a hypoestrogenic state. (ii) Reduction of the growth hormone (GH) release stimulated by GH-releasing hormone. (iii) Inhibition of neoangiogenesis by affecting vascular endothelial growth factor and basic fibroblastic growth factor. (iv) Reduction of the basal rate of coagulatory processes. Improvement in fibrinolytic reactivity. (v) Altered vascular resistance index, pulsatility index, vascular peak velocity, and possible immune response. (vi) Reduction of the degree of inflammation post-operatively.	–	–	Wright and Sharpe-Timms (1995)	–	Baysal (2001), Imai *et al.* (2003), Schindler (2004)	–
Calcium channel blockers	Anti-inflammatory actions	–	–	Steinleitner *et al.* (1988, 1989, 1990)	–	–	–
Anti-coagulants Heparin	Interaction with antithrombin III in the clouding cascade or direct stimulation of the activity of plasminogen activators	–	–	Tayyar *et al.* (1993), Diamond *et al.* (1991a,b)	–	Jansen (1988), Reid *et al.* (1997)	Fayez and Schneider (1987)
Fibrinolytic agents Plasmin preparations Plasmin activators	Direct action: reduction of the fibrinous mass Indirect action: stimulation of plasminogen activator activity	Hellebrekers *et al.* (2000)	–	Hellebrekers *et al.* (2000)	–	Hellebrekers *et al.* (2000)	–
Antibiotics	Prophylaxis against infections and hence the inflammatory response that triggers the adhesion formation	Gutmann and Diamond (1992), Gutmann *et al.* (1995)	–	–	–	–	–

Table V. Barrier adjuvants to prevent and/or decrease adhesion formation

Material	Trade name	Mechanism(s) of action	Clinical gynaecological setting
Solid barriers			
Oxidized regenerated cellulose	Interceed (TC7)	Transformation into a gelatinous mass covering the damaged peritoneum	Laparotomic procedures
Intra-abdominal instillates			
Crystalloids Normal saline solution Ringer's lactate		Mechanical separation of raw peritoneal surfaces Cleansing of the fibrin exudate that can serve as a matrix for fibroblast and capillary formation	Laparotomic procedures Laparoscopic procedures
Icodextrin	ADEPT	Rapid metabolism to glucose by the α-amylase in the systemic circulation; slow absorption from the peritoneal cavity	Laparotomic procedures; Laproscopic procedures
Hyaluronic acid (HA)	Intergel	Transformation into a highly viscous solution coating serosal surfaces and minimizing desiccation (application before injury)	Laparotomic procedures
	Hyalobarrier	Transformation into a highly viscous gel through an auto-cross linking process. Coating of incisions and suture materials	Laparotomic procedures Laparoscopic procedures
Solution of HA	Sepracoat	Transformation into a viscous liquid or gel coating serosal surfaces and minimizing desiccation (application before injury)	Laparotomic procedures
Viscoelastic gel	Oxiplex/AP	Transformation into a viscous gel coating surgical sites with a single layer	Laparoscopic procedures
Hydrogel	Spraygel	Solidification after spraying into a gel strongly adherent to the sites of application	Laparotomic procedures Laparoscopic procedures
Fibrin selants	Beriplast	Rolled fibrin sheets to be placed on surgical wounds	Laparotomic procedures Laparoscopic procedures

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 'hydroflotation' effect has represented the most popular and economic agent used for adhesion prevention in gynaecological surgery. However, a meta-analysis of clinical trails has shown that crystalloids 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 crystalloid 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 collegues (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 adhesiolysis.

Currently, there is insufficient evidence to recommend the use of such agent in the adhesion prevention in laparoscopic gynaecological surgery (Metwally *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 bioadsorbable. Intraperitoneal instillation coats serosal surface, minimizes serosal dessication 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 (Johnoson & Johnson Gynecare 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. Sepracoat 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 Sepracoat 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 Sepracoat 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), Lundorff *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 administrated 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-epitheliazed (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 progestasert intrauterine system (IUS) seem to have a too small surface area to prevent adhesion

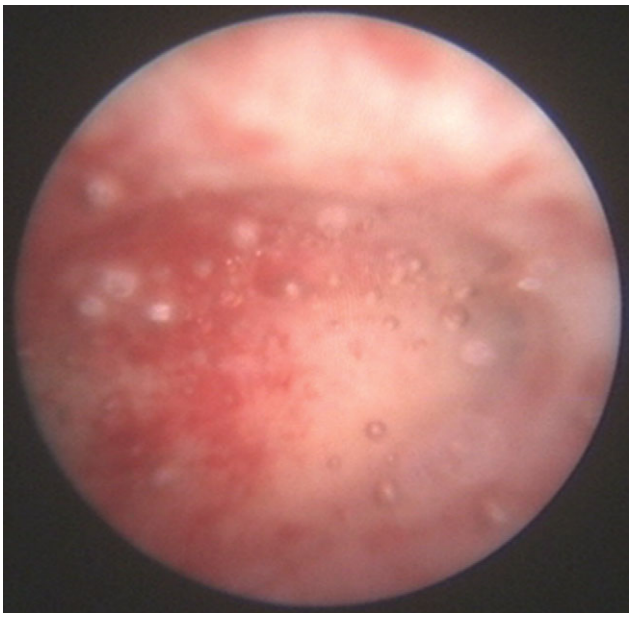

Figure 1. Hysteroscopic view of the uterine cavity distended by the auto-cross linked hyaluronic acid (ACP) gel applied at the end of the hysteroscopic procedure through the out-flow channel of the resectoscope, whereas the surgeon progressively limits the entering of the distension medium through the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

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 ballon. 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 osthia 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 ACP 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 ACP gel following hysteroscopic adhesiolysis significantly reduces the reformation of postoperative IUA. Furthermore, ACP gel was associated with a significant reduction of the severity of IUA. In a further randomized controlled study, Guida *et al.*, (2004) showed that ACP also significantly reduces the incidence and severity of *de novo* formation of IUA after resectoscopic removal of myomas, polyps and septa.

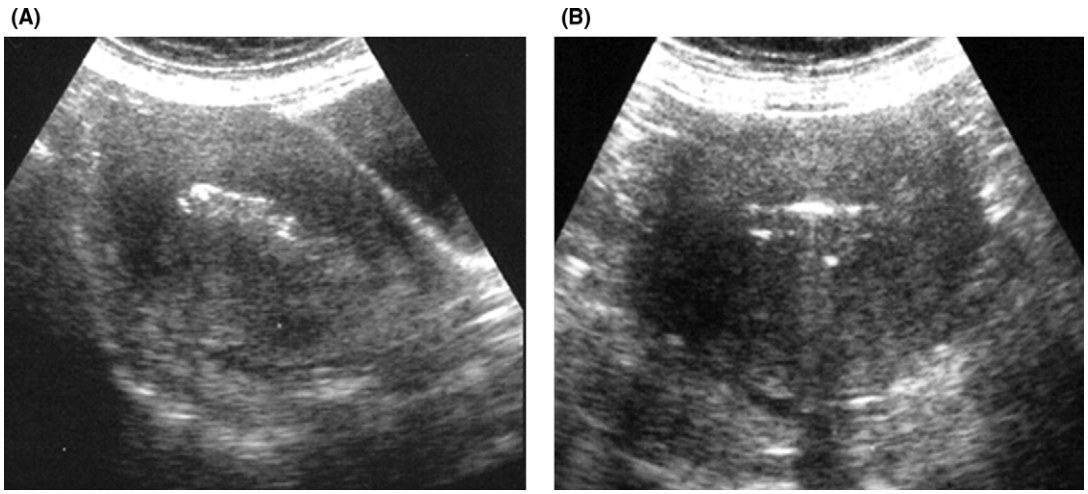

Figure 2. Ultrasonographic image of APC gel remaining in the uterine cavity after 24 h (**A**) and 72 h (**B**).

The real effect of the prevention of IUA 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 IUA 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 postoperative 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 adjunctive 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 pharmacologic adjuvants in conjunction with a barrier material tailored to the specific operative procedure and a precise surgical technique.

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