

Adhesion prevention in endometriosis: a neglected critical challenge

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- Pr H. Roman, Rouen

The first congress of the “Society of Endometriosis and Uterine Disorders” (SEUD) has been designed to provide an innovative and comprehensive overview of the latest research developments in endometriosis, in uterine disorders and in women’s reproductive life fields. Many distinguished scientists from all over the world took part to this congress and shared the latest data and their experience. This first congress has been a frank success with a strong attendance and with meaningful exchanges.

This paper focuses on key issues regarding adhesion prevention in endometriosis.

ADHESION RISKS AFTER ENDOMETRIOSIS SURGERY

From the intervention of Dr M. Wallwiener, University Hospital of Heidelberg, Germany

Facts on adhesions burden and pathogenesis

Post-surgical adhesions are abnormal fibrous connections developing between the peritoneum and organs (Wallwiener-2014). In abdominal and pelvic surgery, adhesion formation must be regarded as the most common post-surgical complication occurring after 60-90% of procedures (Menzies-1990; Hirschelmann-2012).

The consequences are chronic pelvic pain, bowel obstruction and infertility due to formation of adnexal adhesions and complications during surgery such as difficult dissection and visceral injury (Hirschelmann-2012; Monk-1994). Adhesion formation is a complex process influenced by various factors. Following peritoneal trauma, fibrin

deposition occurs. When balance between fibrin deposition and fibrinolysis is impaired, fibrin strands occur and stable adhesions are subsequently formed (Hirschelmann-2012).

Surgical risk factors of adhesion formation are presented in table 1.

► *Table 1: Surgical risk factors of adhesion formation (Hirschelmann-2012; ASRM-2008)*

Ischemia
Tissue desiccation
Electrocoagulation
Sutures
Pneumoperitoneum
Infection
Foreign body

Post-surgical adhesions: How do European Surgeons consider the impact of adhesions?

Answers are based on the ANGEL Awareness Study (ANti-adhesions in Gynecology Expert panel) (Wallwiener-2014).

This survey was conducted in 2012 and 2013 among gynaecological surgeons from several European countries to assess the actual knowledge and practice related to postsurgical adhesions and measures for reduction. Four hundred and fourteen gynaecological surgeons from 36 European countries working in a variety of care settings answer an 18-item online questionnaire.

More than 70% of participants agreed that post-surgical adhesions are a source of major morbidity and 44% declared that they regularly used anti-adhesion agents.

About 65% of responders declared they provide information to their patients regarding the risk of adhesion formation and possible complications of adhesions. For 41% of survey participants, laparotomic interventions were associated with a risk of post-

surgical adhesions and they were fewer to associate this risk with laparoscopic interventions (19%). Most cited risk factors are listed in table 2.

► *Table 2: Type of surgery and parameters influencing adhesion formation most cited by responders (ANGEL survey)*

Type of surgery	Parameters
<ul style="list-style-type: none">• Endometriosis surgery• Myomectomy• Adhesiolysis• Adnexal surgery• Hysterectomy• Ectopic pregnancy• Caesarean section	<ul style="list-style-type: none">• Infection within abdomen• Extensive tissue trauma• Post-operative infection• Previous surgeries

According to responses, endometriosis surgery and myomectomy represent the highest risk of adhesion formation.

ADHESION RISKS AFTER ENDOMETRIOSIS SURGERY

❖ First priority: PREVENTION

Almost all gynaecological surgeons (94.8% of responders) considered that good surgical practice was important to prevent post-surgical adhesions; they were 60.5% and 55.3%, respectively, to consider anti-adhesive barriers and peritoneal conditioning (temperature, gas environment, and the

type of irrigation fluid) as important.

In conclusion, participants in this survey had a good knowledge of factors causing adhesions. However, knowledge of surgical techniques recommended and use of anti-adhesion agents developed to reduce adhesions need to be improved.

Which strategies to reduce postoperative adhesions?

None of pharmacologic agents (e.g. anti-inflammatory, fibrinolytics, anticoagulants...) used to prevent the formation of adhesions has been found to be effective (Pados-2010). Recommended options to reduce

adhesion formation are listed in the table 3 below.

These strategies should be adopted and implemented, especially in high-risk surgery such as endometriosis surgery (ESGE-2014).

► Table 3: Strategies to reduce postoperative adhesions (EGSE-2014, Pados-2010)

1. Minimizing peritoneal injury during surgery	Careful surgical technique: microsurgical principles, gentle tissue handling
	Meticulous hemostasis
	Excision of necrotic tissue
	Avoiding ischemia and desiccation
2. Prevention of exposure to foreign materials	Using non-reactive suture materials
	Avoiding contamination with surgical glove powder
	Prevention of infection
3. Use of anti-adhesive agents	

Adhesion prevention in endometriosis

Despite the lack of data on the impact of adhesiolysis on adhesions-related symptoms such as fertility, pelvic pain or disease recurrences or other adhesions-related complications in women with endometriosis, anti-adhesive barriers should be considered in high risk patients such as endometriosis.

Future studies are required, focusing on a 2-step strategy that includes measures applied at the time of surgery and subsequent administration of agents able to prevent the development of new adhesions in order to analyze the impact on fertility and other long-term outcomes.

STRATEGIES FOR REDUCING ADHESIONS IN ENDOMETRIOSIS RESECTION: WHICH PLACE FOR THE GELS AGENTS?

From the intervention of Pr H. Roman, CHU of Rouen

Scientific data

The Cochrane review published in 2014 (Ahmad-2014), analyzed 29 trials and concluded that gels and liquid anti-adhesive agents are effective in preventing adhesions in gynaecologic surgery at second look laparoscopy. Data also showed that anti-adhesive gels were more efficacious than liquid agents (cf. table 4).

Another Cochrane review published in 2015 (Ahmad-2015) focused on clinical endpoints and found insufficient data to show effects of anti-adhesive agents on chronic pelvic pain or fertility outcomes in women of reproductive age. Further research is thus warranted.

In the field of endometriosis surgery, 3 randomized, comparative trials have shown partial efficacy of anti-adhesive agents in reducing adhesions at second look laparoscopy. However, data on clinical outcome such as pelvic pain, fertility or disease recurrence is lacking (Somigliana-2012).

In conclusion, anti-adhesive agents are efficacious to reduce adhesion formation for gynaecologic surgery in women with or without endometriosis, but clinical trials are needed to collect data on outcomes such as fertility and chronic pelvic pain.

► *Table 4: Efficacy data (at second look laparoscopy) of anti-adhesive agents in gynaecologic surgery - Cochrane review (Ahmad-2014).*

	Odds-ratio	95% CI	p	Evidence level
75% reduction of adhesion formation with anti-adhesive gel in comparison with no treatment (2 trials, 134 patients)	0.25	0.11 - 0.56	0.0006	High
Anti-adhesive gels are 64% more efficacious than liquid agents (2 trials, 342 patients)	0.36	0.19 - 0.65	0.001	High

Medico-economic issues

From data of a Scottish study involving 29,790 patients managed by open surgery and followed up for 10 years, consequences of adhesion on morbidity were important: overall, 34.6% of patients who underwent abdominal or pelvic surgery were readmitted for a disorder directly or possibly related to adhesions (Ellis-1999). A British study based on an economic model, estimated that the use of an anti-adhesive agent with a cost of 130 euros and efficacy of 25 % for 1 year could save over 40 million euros during 10 years period (Wilson-2007).

A prospective medico-economic trial would be extremely extensive: in order to show a 50% reduction of readmissions (from 5% to 2.5%) such a trial should include 2 000 patients (1,000 in each arm) followed up for 5 to 10 years.

These trial hypothesis emphasize the major difficulty for setting up such studies. Furthermore, the inclusion criteria to be used needs to be discussed: which procedures to do and which type of endometriosis to include.

Main results: anti-adhesive agents / endometriosis surgery

A trial in 37 patients showed that in comparison with no treatment, the use of the anti-adhesive gel Oxiplex®/AP caused a significant reduction of the AFSr subscore evaluating the adnexal adhesions (decrease of the AFSr subscore from 8.4 to 6.2 for Oxiplex®/AP versus increase of the AFSr subscore from 10 to 14 in the control arm, p<0.01) (diZerega-2007).

In 32 patients with severe endometriosis who underwent endometriosis surgery and adhesiolysis, the use of Interceed® (Oxydated regenerated cellulose) was efficacious to prevent adhesion formation assessed by a second look laparoscopy 12-14 weeks after surgery. Twelve of 16 (75 %) were free of adhesion compared with two of 16 (12.5%) in the control arm; p<0.05) (Mais-1995).

STRATEGIES FOR REDUCING ADHESIONS IN ENDOMETRIOSIS RESECTION: WHICH PLACE FOR THE GELS AGENTS?

However, efficacy data of Adept® (4% icodextrin solution) are disappointing. In the subgroup of women with endometriosis (n=241) in a trial comparing Adept® to a Ringer lactate solution, only the most severe patients (more than 6 sites treated) benefited from Adept® (Brown-2007). Another trial including 76 patients who underwent endometriomas surgery did not show any difference on adhesion prevention between Adept and a Ringer lactate solution (Trew-2011).

The European Society of Human Reproduction and Embryology (ESHRE) proposed recommendation on the management of women with endometriosis. The table 5 summarizes the recommendations on adhesion prevention (ESHRE-2013)

► *Table 5: Recommendations on the use of anti-adhesive agents in the surgery of women with endometriosis (ESHRE-2013)*

Clinicians can use oxidised regenerated cellulose during operative laparoscopy for endometriosis, as it prevents adhesion formation	Grade B
It is not reasonable for clinicians to use icodextrin after operative laparoscopy for endometriosis to prevent adhesion formation, as no benefit has been shown	Grade B
The group recommend that clinicians should be aware that other anti-adhesion agents (polytetrafluoroethylene surgical membrane, hyaluronic acid products) have been studied and proven effective for adhesion prevention in the context of pelvic surgery, although not specifically in women with endometriosis	Expert opinion

Hyalobarrier® scientific data

Hyalobarrier® is an auto-cross linked Hyaluronic acid gel with higher adhesivity and prolonged residence time on the injured surface (Nappi-2007).

Efficacy of Hyalobarrier® has been shown in a trial that included 36 patients who underwent a laparoscopic myomectomy. At the second look laparoscopy performed 2-3 months later, 28% of the treated patients had adhesions in comparison with 78% in the control arm (p<0.01) (Pellicano-2003).

In an extension study, these women were then followed up to assess their pregnancy rate. One year after the surgery, significantly more women were

pregnant in the Hyalobarrier® arm (78%) in comparison with the control arm (39%; p<0.01) (Pellicano-2005).

...❖ Efficacy of Hyalobarrier® on intra-uterine adhesions

A trial in 132 patients evaluated the efficacy of Hyalobarrier® to prevent *de novo* intra-uterine adhesions after hysteroscopic surgery (resection of polyps, myomas or uterine septa). Hyalobarrier® significantly reduced the development of *de novo* adhesions at 3 months follow-up. Furthermore, the staging of adhesions showed a significant decrease in adhesion severity in patients treated with Hyalobarrier® (Guida-2004). Another study included 92 patients who underwent hysteroscopic adhesiolysis. Again, the use of Hyalobarrier® reduced significantly the number and severity of intra-uterine adhesions at 3 months follow-up (Acunzo-2003).

...❖ Own experience

Pr Roman shares its personal experience with Hyalobarrier®: in a prospective cohort of 124 women with ovarian endometriomas and severe endometriosis, 42% had colorectal endometriosis and 68% of patients received Hyalobarrier® (Roman-2015)

Fertility outcomes among women wishing to conceive were good with an overall pregnancy rate of 61.4%:

- Spontaneous conception in 64.7% of women
- Successful IVF in 35.3 %

These encouraging results can be reasonably related to endometrioma ablative sparing procedure and adhesion prevention.

Conclusion

The risk of developing adhesions after gynecologic surgery is high and their consequences are important especially in women with endometriosis. Adhesions may be prevented following good surgical practices and use of anti-adhesive agents who demonstrated their efficacy. Furthermore, information for patients concerning the risk and possible consequences of adhesion should be provided.

BIBLIOGRAPHY

- Wallwiener M, *et al.* for The Anti-Adhesions in Gynecology Expert Panel (ANGEL). A European survey on awareness of post-surgical adhesions among gynaecological surgeons. *Gynecol Surg* 2014;11:105-112.
- Menzies D, Ellis H. Intestinal obstruction from adhesions-how big is the problem? *Ann R Coll Surg Engl* 1990;72(1):60-3.
- Hirschelmann A, *et al.* A review of the problematic adhesion prophylaxis in gynaecological surgery. *Arch Gynecol Obstet* 2012;285:1089-97.
- Monk BJ, *et al.* Adhesions after extensive gynecologic surgery: clinical significance, etiology, and prevention. *Am J Obstet Gynecol* 1994;170:1396-403.
- Practice Committee of American Society for Reproductive Medicine in collaboration with Society of Reproductive Surgeons. Pathogenesis, consequences, and control of peritoneal adhesions in gynecologic surgery: a committee opinion. *Fertil Steril* 2013;99:1550-5.
- De Wilde RL, *et al.* Consensus recommendations on adhesions (version 2014) for the ESGE Adhesions Research Working Group (European Society for Gynecological Endoscopy): an expert opinion. *Arch Gynecol Obstet* 2014;290:581-2.
- Pados G, *et al.* Prevention of intra-peritoneal adhesions in gynaecological surgery: theory and evidence. *Reprod Biomed Online* 2010;21:290-303.
- Ahmad G, *et al.* Fluid and pharmacological agents for adhesion prevention after gynaecological surgery. *Cochrane Database Syst Rev* 2014;7:CD001298.
- Ahmad G, *et al.* Barrier agents for adhesion prevention after gynaecological surgery. *Cochrane Database Syst Rev* 2015;4:CD000475
- Somigliana E, *et al.* Adhesion prevention in endometriosis: a neglected critical challenge. *J Minim Invasive Gynecol*. 2012;19:415-21.
- Ellis H, *et al.* Adhesion-related hospital readmissions after abdominal and pelvic surgery: a retrospective cohort study. *Lancet* 1999;353:1476-80.
- Wilson MS. Practicalities and costs of adhesions. *Colorectal Dis* 2007;9 Suppl 2:60-5.
- diZerega GS, *et al.* Clinical evaluation of endometriosis and differential response to surgical therapy with and without application of Oxiplex/AP* adhesion barrier gel. *Fertil Steril* 2007;87:485-9.
- Brown CB, *et al.* Adept (icodextrin 4% solution) reduces adhesions after laparoscopic surgery for adhesiolysis: a double-blind, randomized, controlled study. *Fertil Steril* 2007;88:1413-26.
- Trew G, *et al.* Gynaecological endoscopic evaluation of 4% icodextrin solution: a European, multicentre, double-blind, randomized study of the efficacy and safety in the reduction of *de novo* adhesions after laparoscopic gynaecological surgery. *Hum Reprod* 2011;26(8):2015-27.
- ESHRE Endometriosis Guideline Development Group. Management of women with endometriosis. September 2013.
- Nappi C, *et al.* Prevention of adhesions in gynaecological endoscopy. *Hum Reprod Update*. 2007;13(4):379-94.
- Pellicano M, *et al.* Effectiveness of autocrosslinked hyaluronic acid gel after laparoscopic myomectomy in infertile patients: a prospective, randomized, controlled study. *Fertil Steril* 2003;80(2):441-4.
- Pellicano M, *et al.* Reproductive outcome after autocrosslinked hyaluronic acid gel application in infertile patients who underwent laparoscopic myomectomy. *Fertil Steril* 2005;83:498-500.
- Guida M, *et al.* Effectiveness of auto-crosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: a prospective, randomized, controlled study. *Hum Reprod* 2004;19:1461-4.
- Acunzo G, *et al.* Effectiveness of auto-cross-linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis: a prospective, randomized, controlled study. *Hum Reprod* 2003;18(9):1918-21.
- Roman H, *et al.* Recurrences and fertility after endometrioma ablation in women with and without colorectal endometriosis: a prospective cohort study. *Hum Reprod* 2015;30(3):558-68.