Current methods for adhesion prevention

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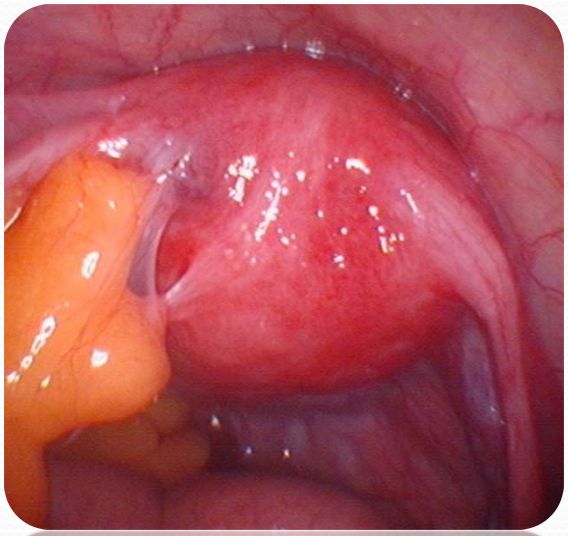
Overview

- Introduction
- Primary prevention
- Secondary prevention

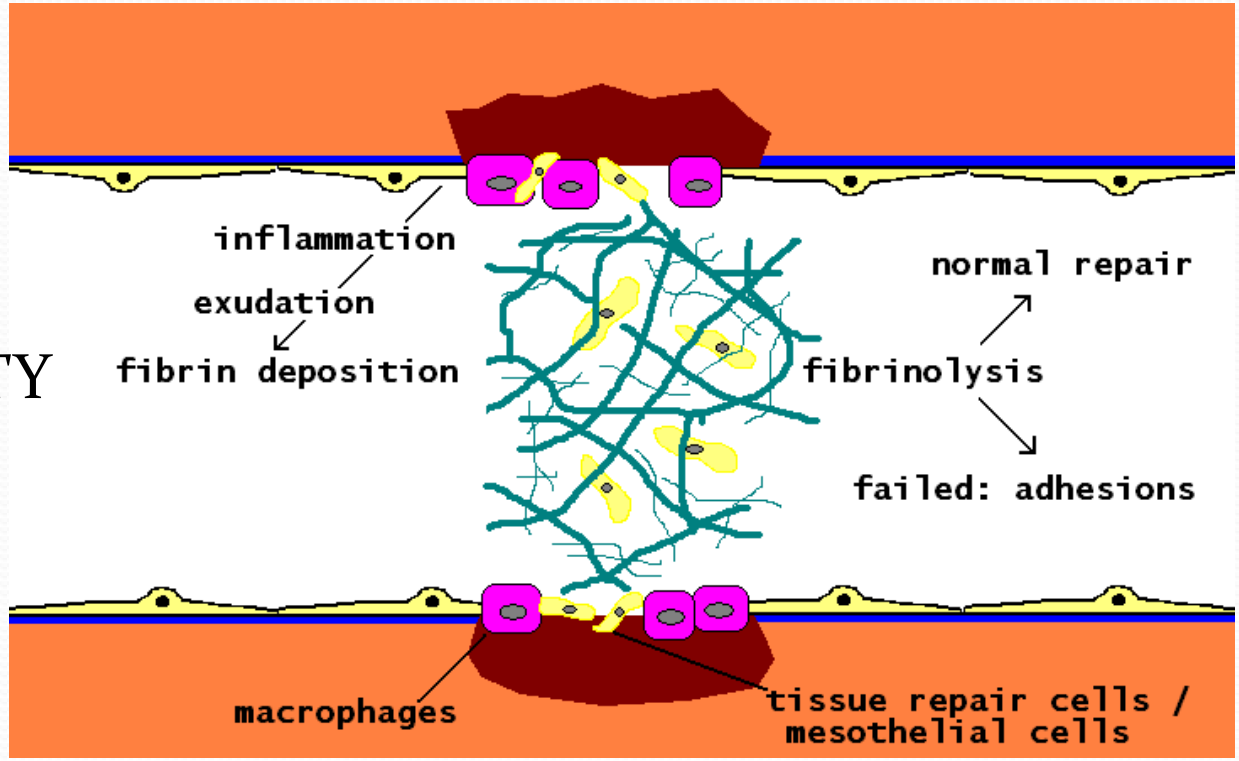
- Take home messages



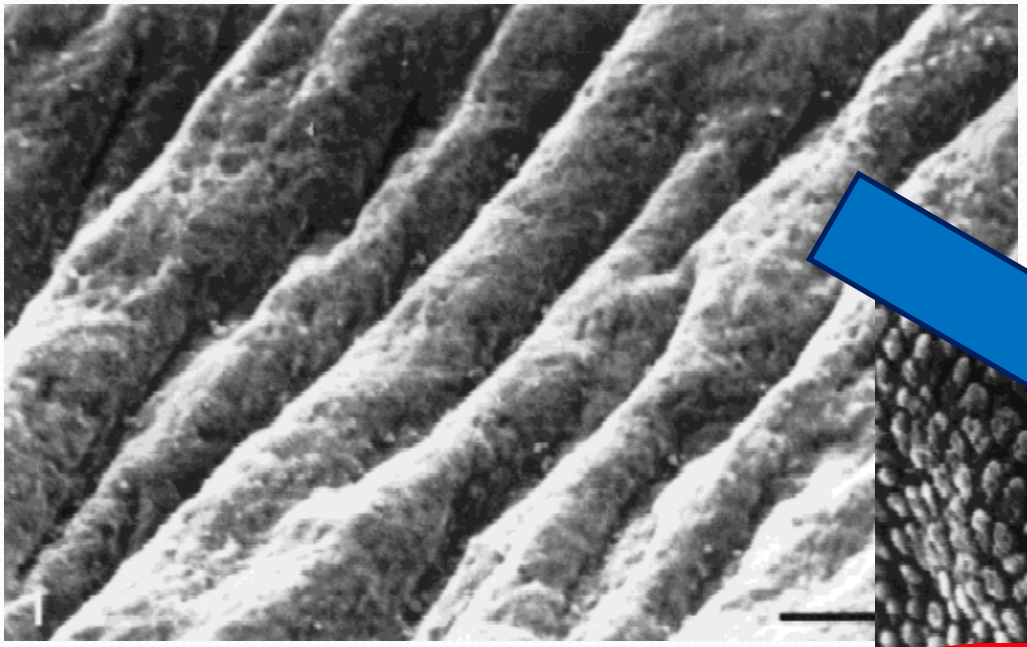
Introduction

Adhesion = consequence of damage

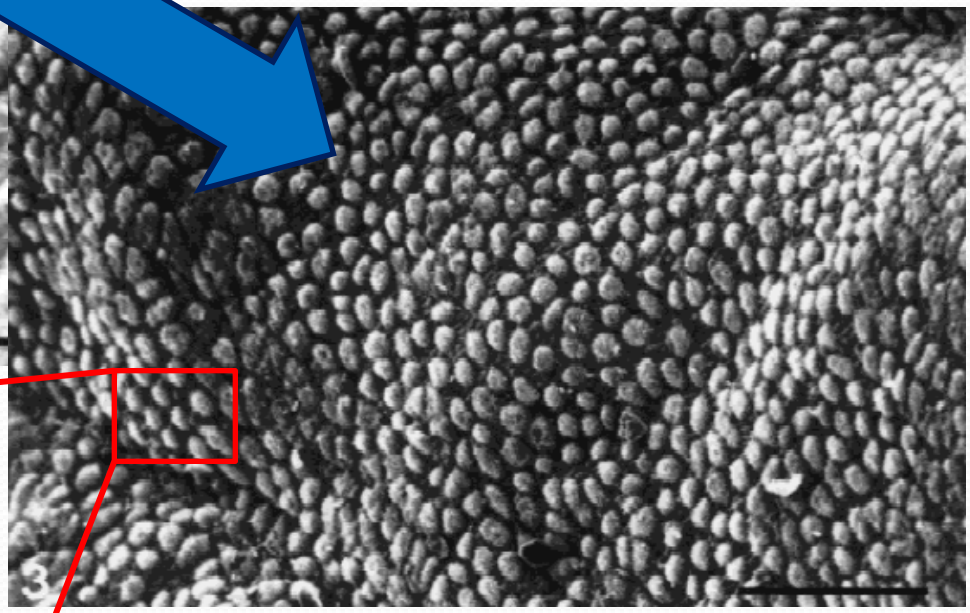
- Damaging the peritoneum bij
  - LOCAL:
    - burning
    - cutting,…
  - WHOLE CAVITY
    - hypoxia
    - dessication
    - manipulation
    - inflammation

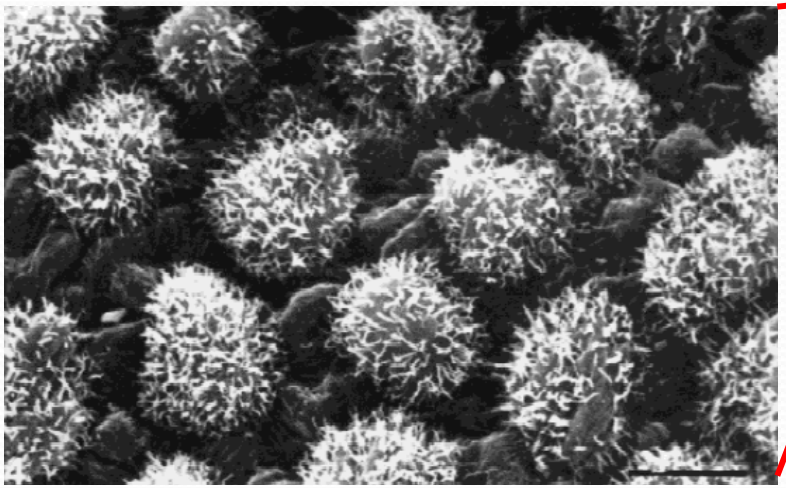


Influence of CO_2 at laparoscopy



60 minutes CO_2



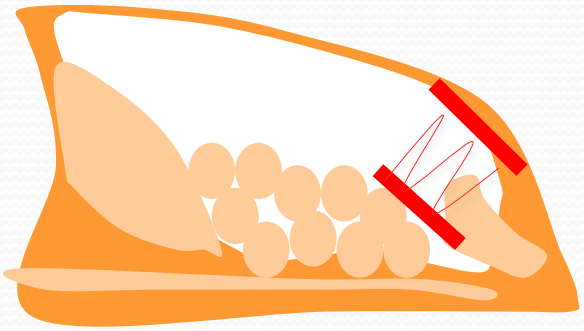


Mesothelial cells

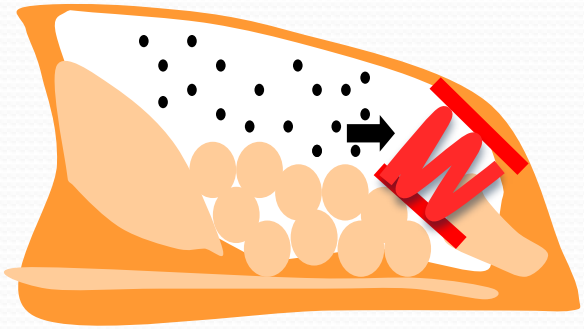
Volz J, Surg Endosc 2009

Adhesion Formation Today

- A local lesion is necessary to start the process



- Factors from peritoneal cavity enhance

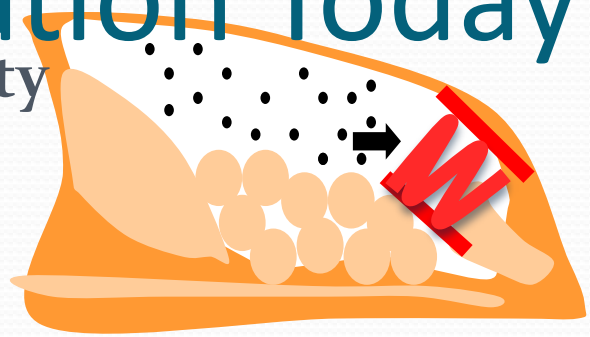


Peritoneal cavity is quantitatively 20 times more important Than local trauma

Surgical Trauma ++++

Adhesion Formation Today

- Factors from peritoneal cavity



mechanical trauma

blood

hypoxia,

hyperoxia,

Desiccation

Acute Inflammation

Lower temperature

New gas mixtures

(oxygen, N20)

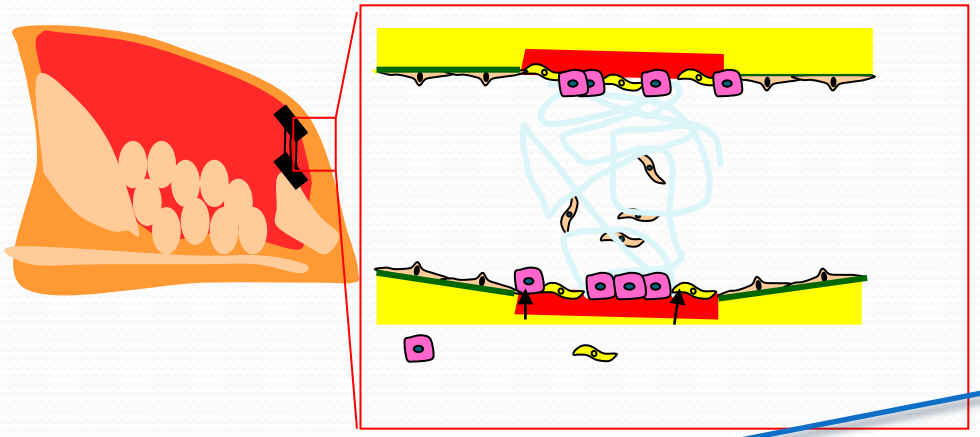
dexamethasone

Bad **Good**

Cumulative effect

Surgical Trauma ++++

The classic Model : a local phenomenon



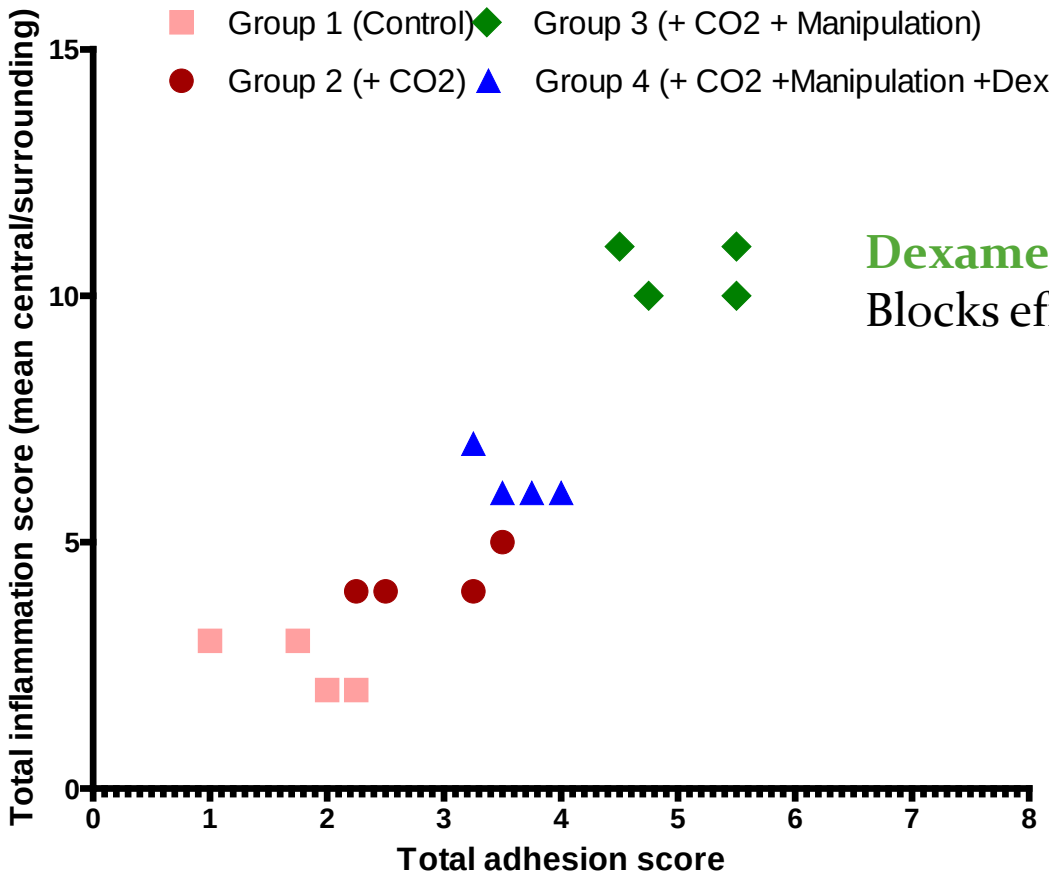
- **Surgical trauma**
  - **Exudation**
    - **Fibrin deposition**

Starts a cascade of events

fibrinolysis

Adhesiolysis
No reformation

Acute inflammation



Dexamethasone:
Blocks effect of manipulations

Prevention strategies

- Primary
  - No trauma to the mesothelium
  - Reduce inflammation
- Secundary
  - Reduce the effect of the trauma

Primary Prevention

Infection related adhesions

- Antibiotics (Bothin, 2003)

- Rinsing (also depletion of residual macrophages)
  - BAD in case of clean surgery (Dunn, 1984)
  - BENEFICIAL (if infection) with:
    - Chlorhexidine (Bondar 2000)
    - Hyaluronic acid (Reijnen 1999)

Dexamethasone

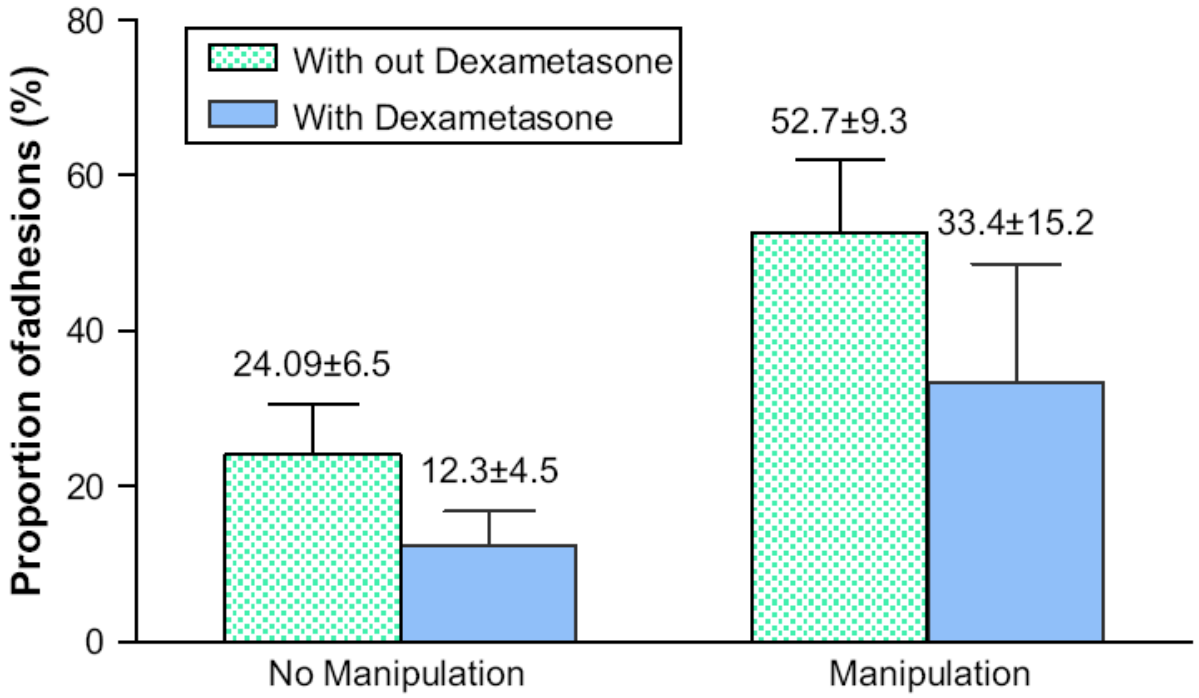


Fig. 3. Manipulation increases (p =.0001 for adhesion proportion) and dexamethasone decreases (p =.0001 for adhesion proportion) adhesion formation in laparoscopic mouse model (2-way ANOVA; proportion). *Bars* present means and SD of each group.

Schonman et al. Effect of Upper Abdomen Tissue Manipulation on Adhesion Formation between Injured Areas in a Laparoscopic Mouse Model, JMIG 2009

Surgery

- Avoid bleeding (more fibrin)
  - Rinse with NaCl, Ringer, Hartman + Heparine 5000 IU/L
- Remove chalk from the gloves
- Serosal damage:
  - Closure of the peritoneum has no advantage, but…

Tulandi T. Closure of laparotomy incisions with or without peritoneal suturing and second-look laparoscopy AJOG 1988

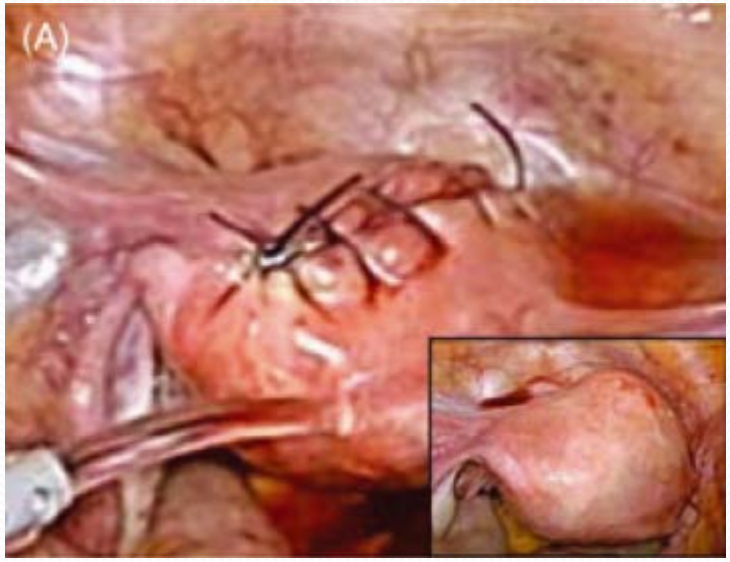
Surgery

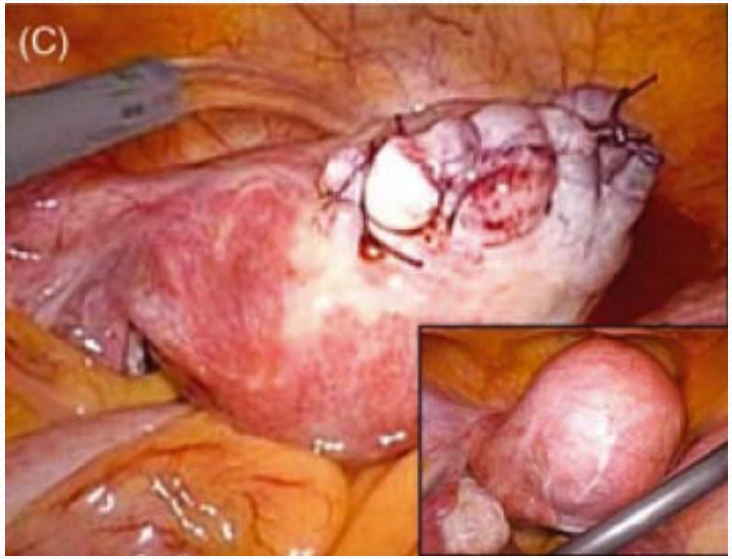
- **Laparoscopy** better then laparotomy

Luciano, Infer Repr Med Clin North Am 1994

Tinelli, Fertil Steril 2011

- Uterine scar: protruding = adhesions





Kumakiri, AOGS 2012

Myomectomy and adhesions

- N= 108 patients with second look laparoscopy

Table 1. Comparisons of uterine status after laparoscopic myomectomy in patients with and without later wound adhesion.

Variable	Patients without adhesion ($n = 67$)	Patients with adhesion ($n = 41$)	p-Value
Total number of wounds (per patient)	2 (1–9)	3 (1–7)	0.01*
Total length of wounds (cm; per patient)	8 (2–23.9)	10 (4.6–17.5)	0.02*
Location of uterine wounds (number of patients)			
Only in anterior wall	15 (22.4%)	8 (19.5%)	0.18
Only in posterior wall	17 (25.4%)	5 (12.2%)	
In both walls	35 (52.2%)	28 (68.3%)	
Patients with protruding wounds	24 (35.8%)	24 (58.5%)	0.02*
Patients with swollen wounds	19 (28.4%)	12 (29.3%)	0.92

Kumakiri et al. AOGS 2012

Preventie: Surgery

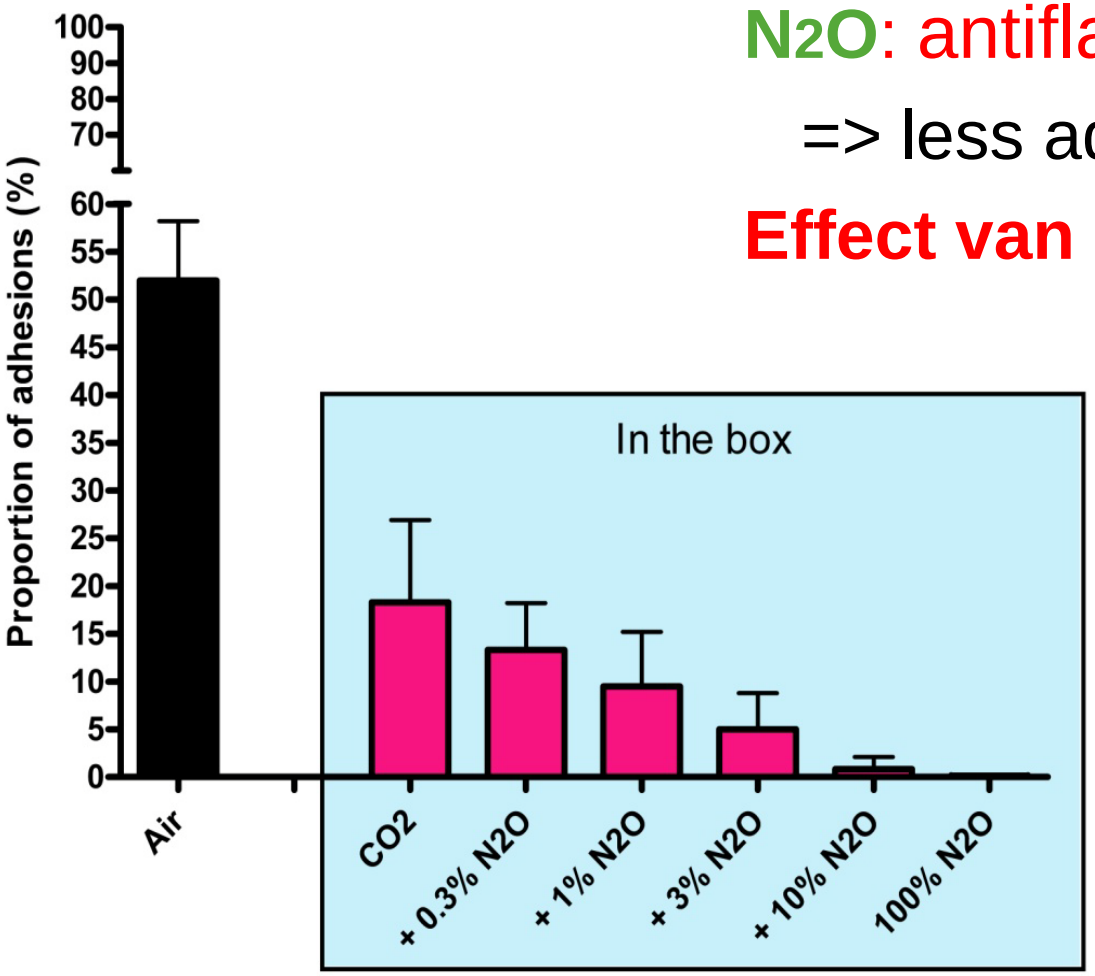
Pregnancy rates at 6 and 12 months after laparoscopic myomectomy in patients treated (group A) or untreated (group B) with autocrosslinked hyaluronic acid gel.

	Group A (n = 18)			Group B (n = 18)		
	Figure-eight sutures (n = 9)	Subserous sutures (n = 9)	Total patients (n = 18)	Figure-eight sutures (n = 9)	Subserous sutures (n = 9)	Total patients (n = 18)
6 mo	2 (22.2%)	6 (66.7%)[a]	8 (44.4%)	1 (11.1%)	3 (33.3%)[b]	4 (22.2%)[c]
12 mo	5 (55.5%)	9 (100%)[d]	14 (77.8%)	2 (22.2%)	5 (55.5%)[e]	7 (38.8%)[f]

[a] $P<.001$ vs. figure-eight sutures in group A at 6 mo.
[b] $P<.01$ vs. figure-eight sutures in group B at 6 mo.
[c] $P<.01$ vs. group A at 6 mo.
[d] $P<.001$ vs. figure-eight sutures in group A at 12 mo.
[e] $P<.01$ vs. figure-eight sutures in group B at 12 mo.
[f] $P<.01$ vs. group A at 12 mo.

Pellicano. Myomectomy and hyaluronic gel: pregnancy rate. Fertil Steril 2005.

Altering the Gas



N_2O: antiflammatory

=> less adhesions

Effect van 10% = 100%

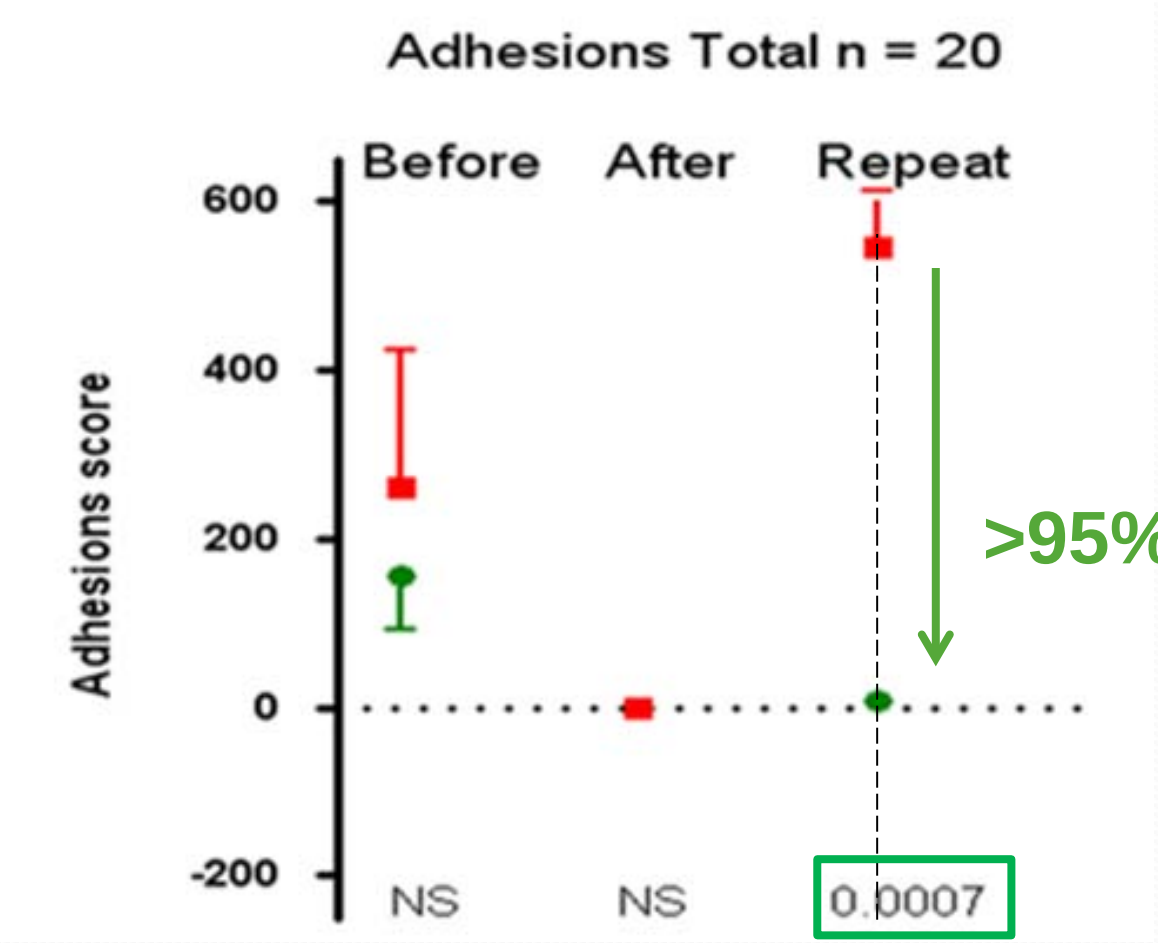
Altering the gas (endometriose)

- Studygroup: **CONDITIONING**
  - Conditioning of the gas: 86%CO_2, **10%N_2O; 4%O_2**
  - No dessication:
    - **100% RH, 32°C**
    - **Sprinkler** (cooling, no condensation)
  - Rinsing with Ringer + heparine
  - Dexamethasone 5mg
  - Hyalobarrier gel

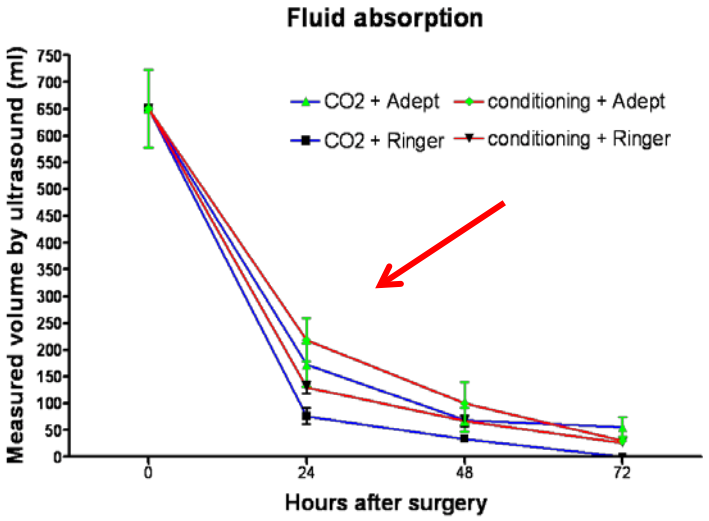
- Relaparoscopy after 2 weeks: *adhesie score*

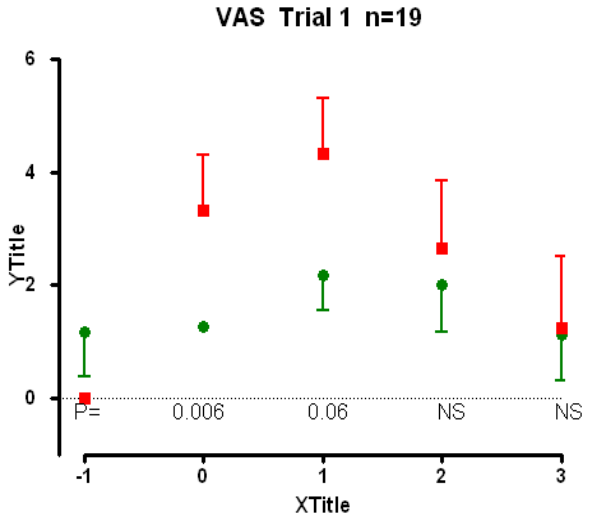
Endometriosis

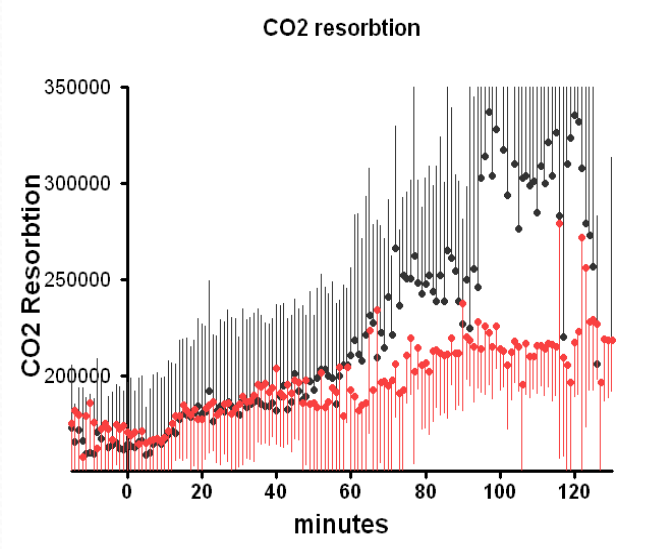
Dexamethasone 5mg
Koninckx' gas
Rinsing with Ringers + heparine
Hyalobarrier Gel Endo



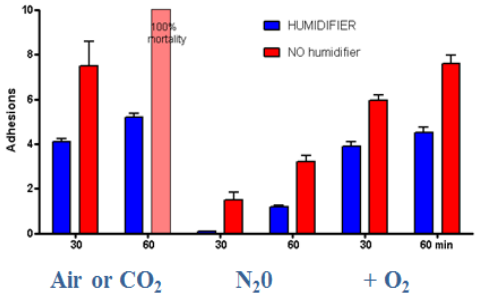
Bonus at CONDITIONING



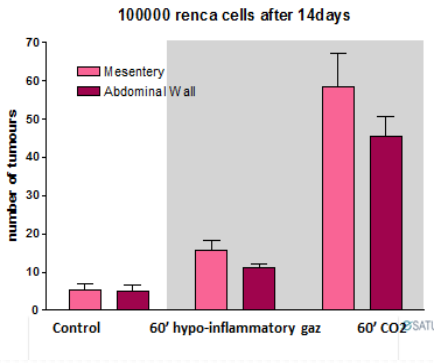




Effect is more important in Open Surgery



Pneumoperitoneum + Oxygen

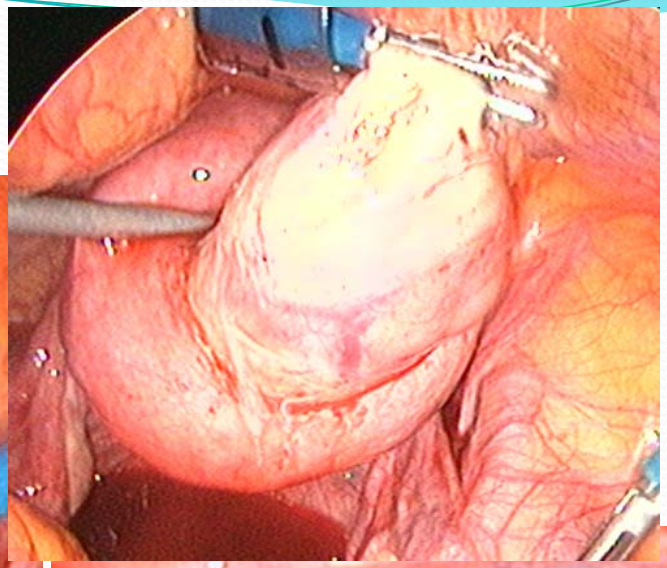


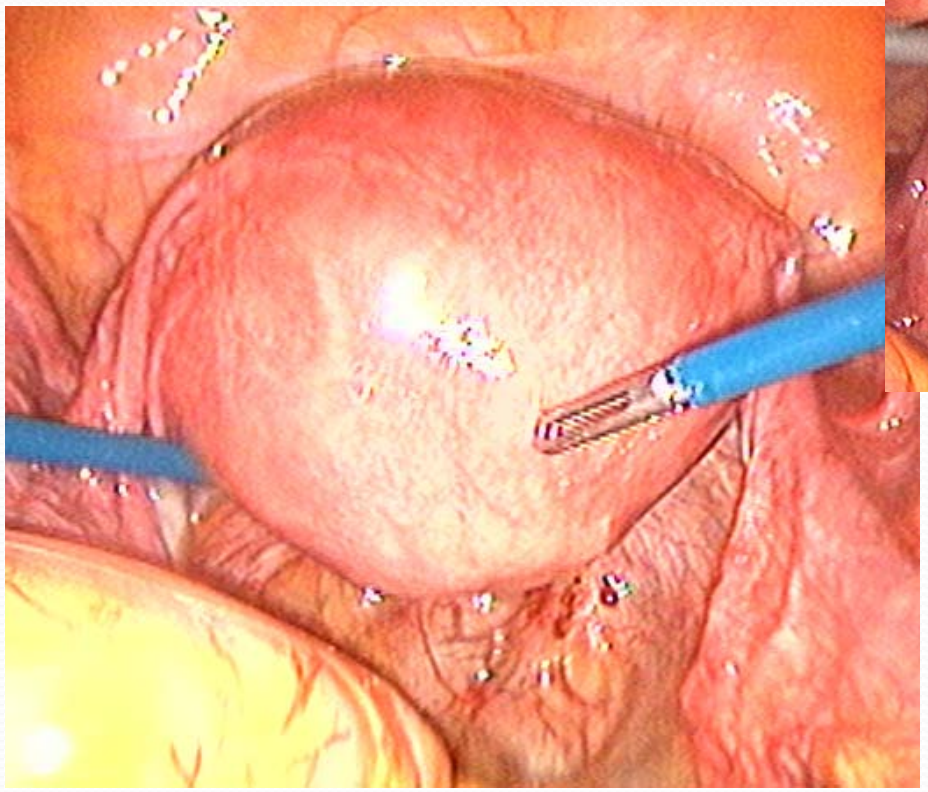
Application at myomectomy

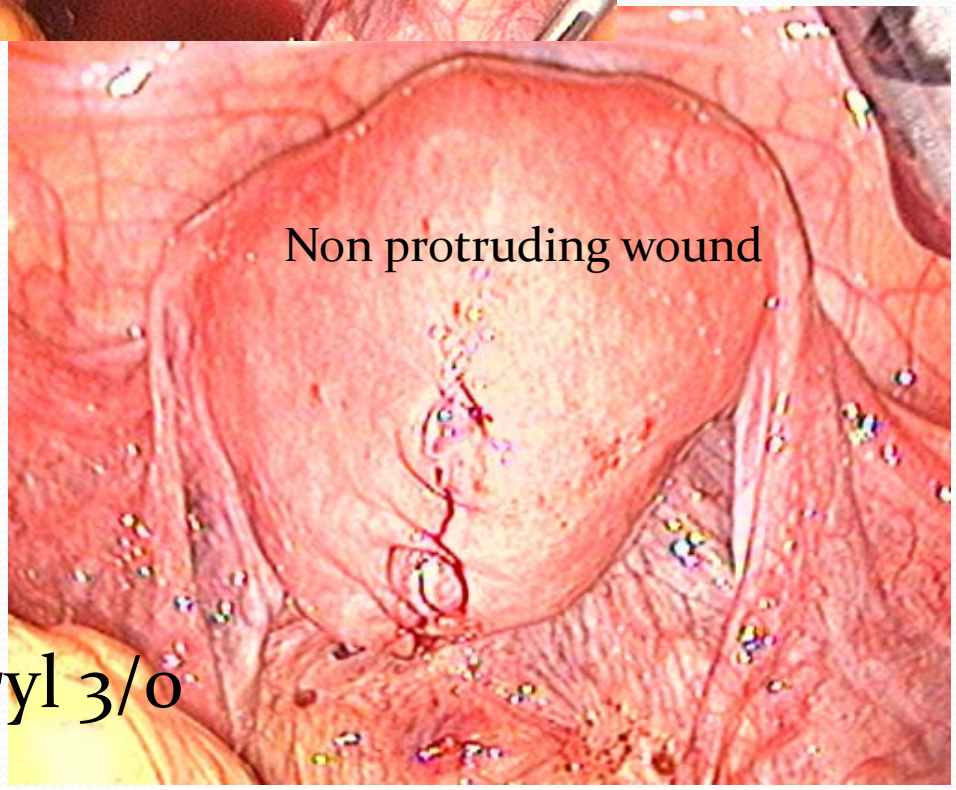
- Ongoing trial at UZ Leuven *ClinTrials.gov: NCT01344486*
- N=40
  - Expected incidence of adhesions from 80±20% to 10±5%
  - With n=40 ⟹ power >90%, p<0,0001
- Assessment of:
  - Post-operative pain
  - Inflammation
  - Resumption of transit

Second look laparoscopy after 2 weeks

Ongoing…



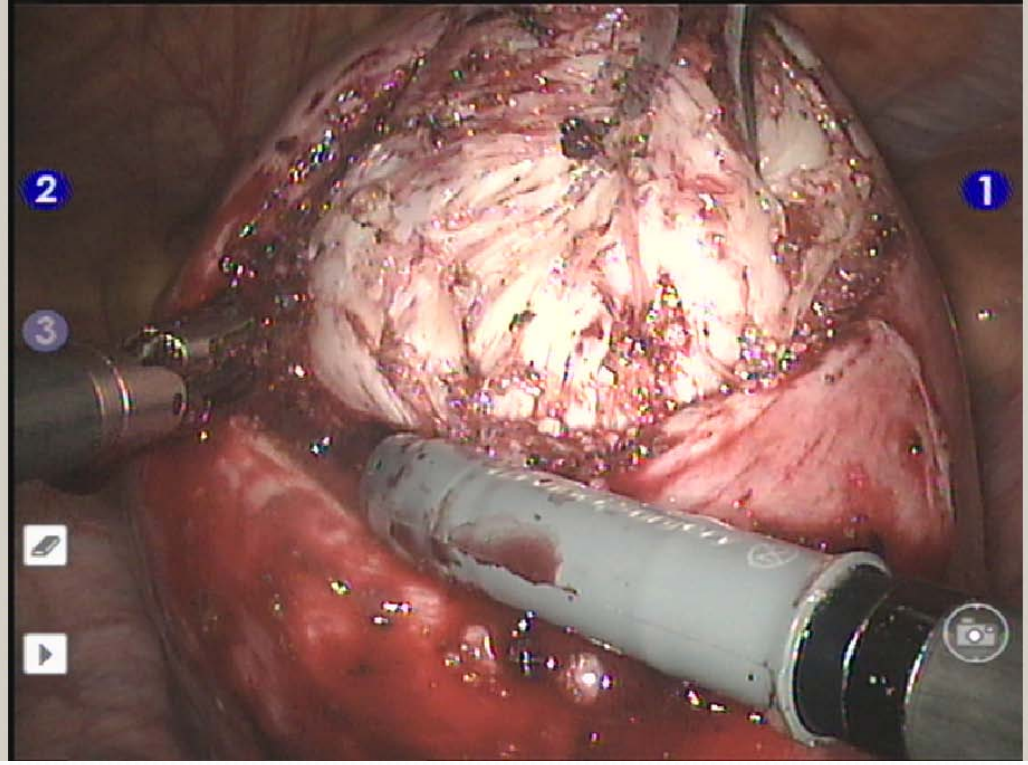




Suture:

V-lock

Monocryl 3/0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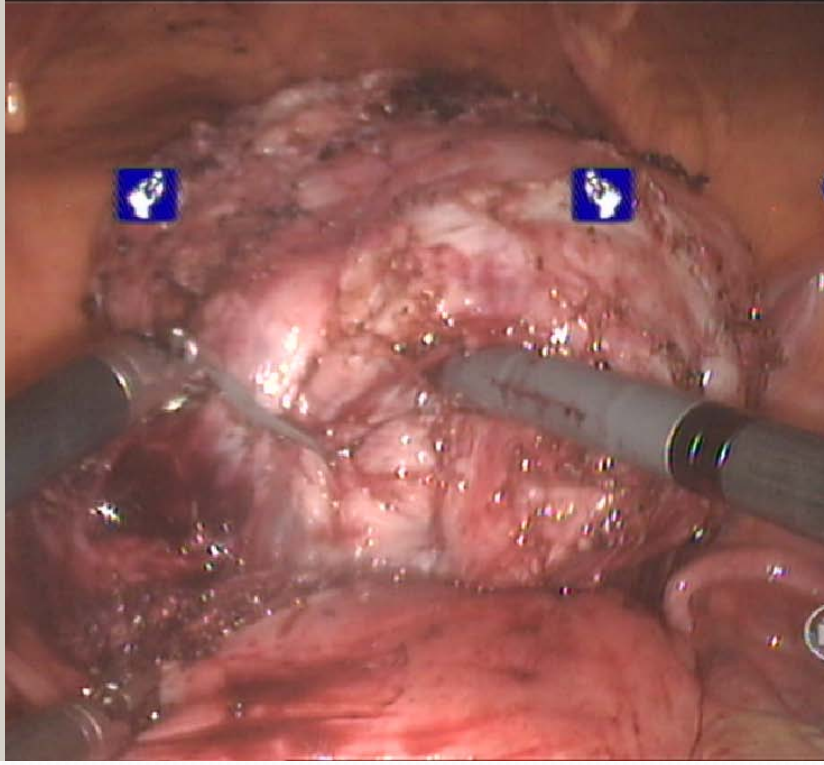
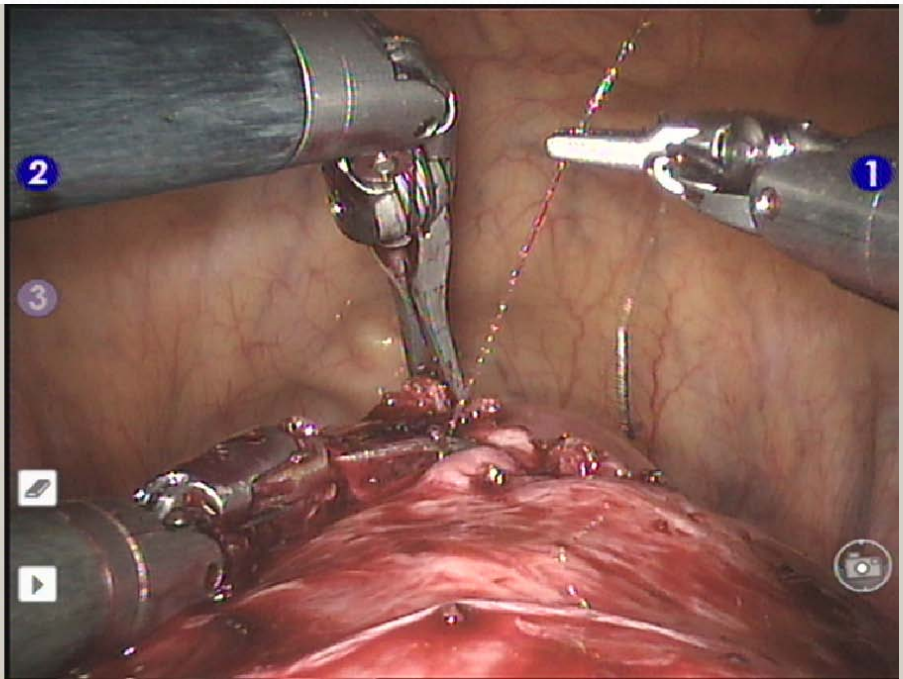
1
3

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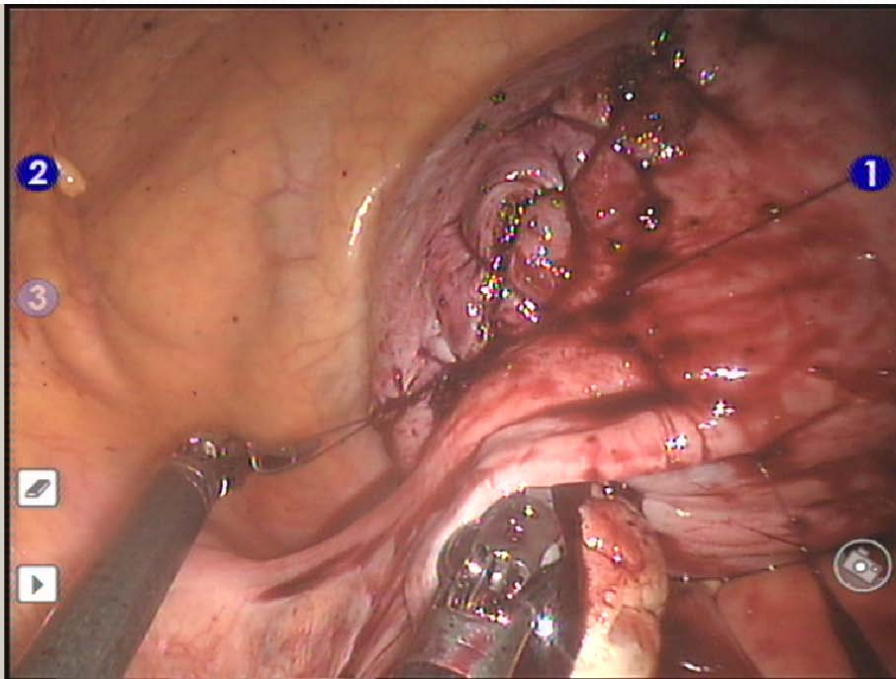
2
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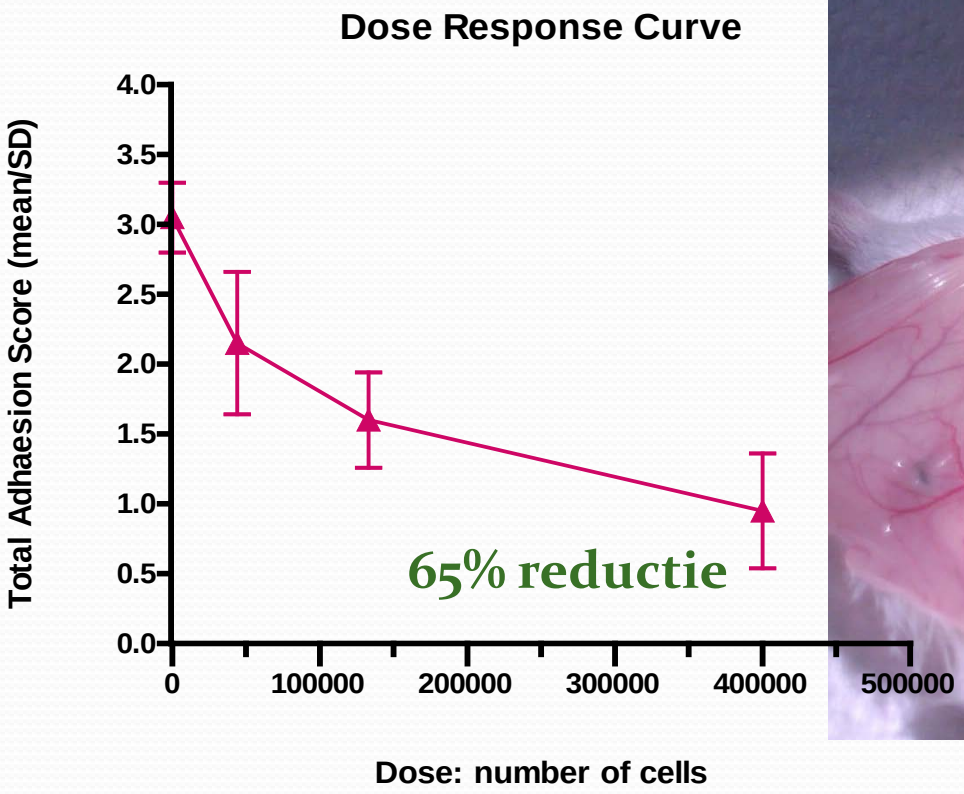
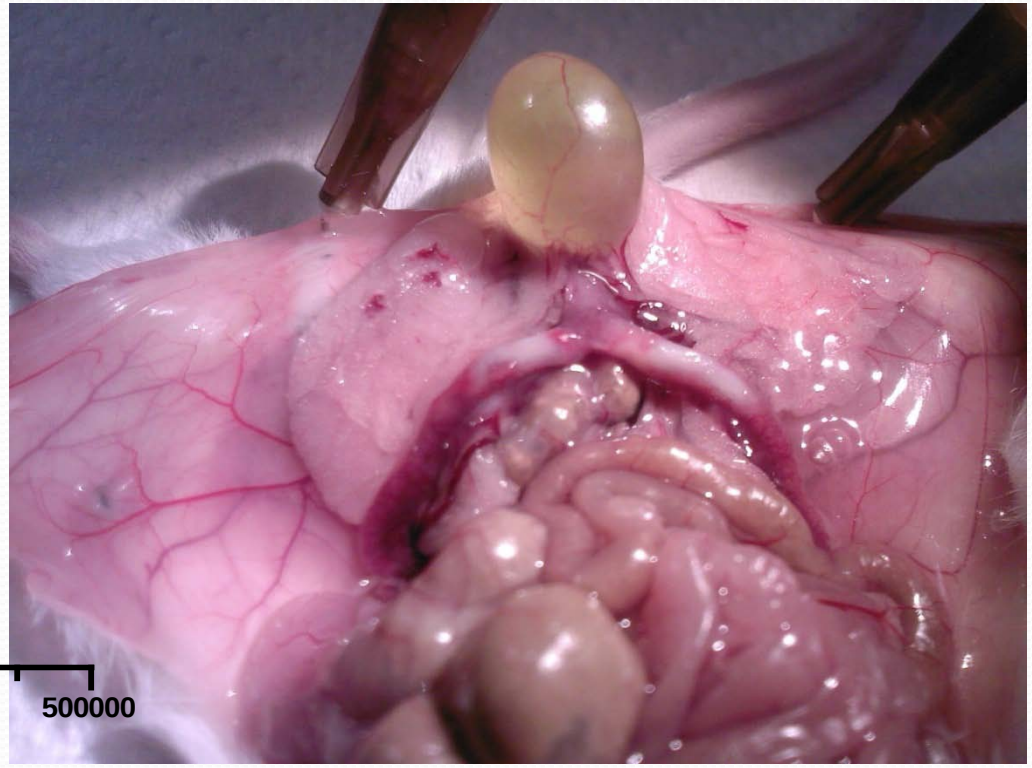
Secondary Prevention

Transplantation of mesothelial cells

- Free floating cells: did not grow
- Adhesions: dose-dependant





Verguts J, et al. Gyn Surg. 2011

Prevention: barriers

- They should be:
  - Safe
  - Effective
  - Easy to use
  - Affordable

They have some effect

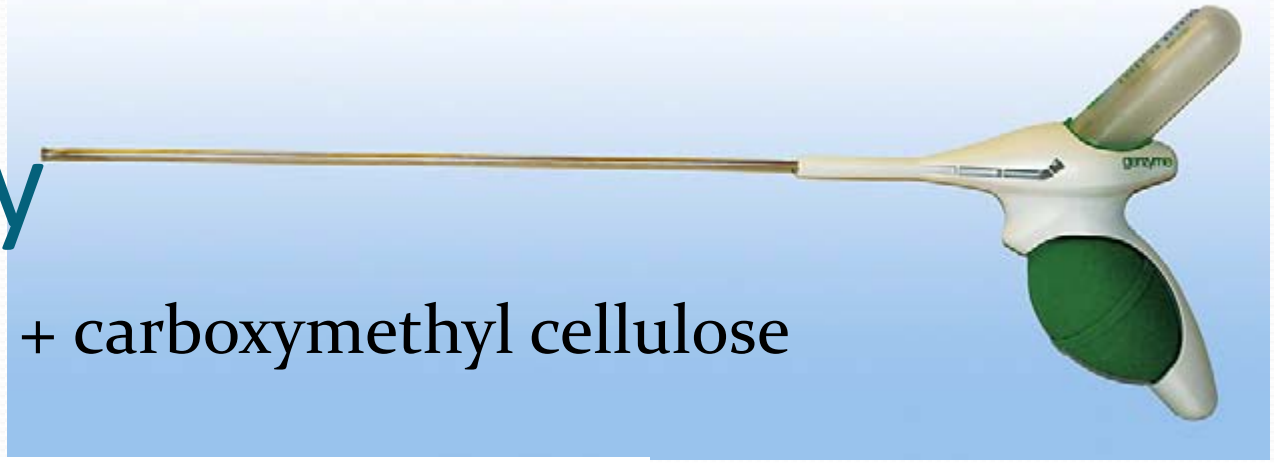
PCT copolymer

- D,L-polylactide-ε-caprolactone-trimethylene carbonate
- N=30

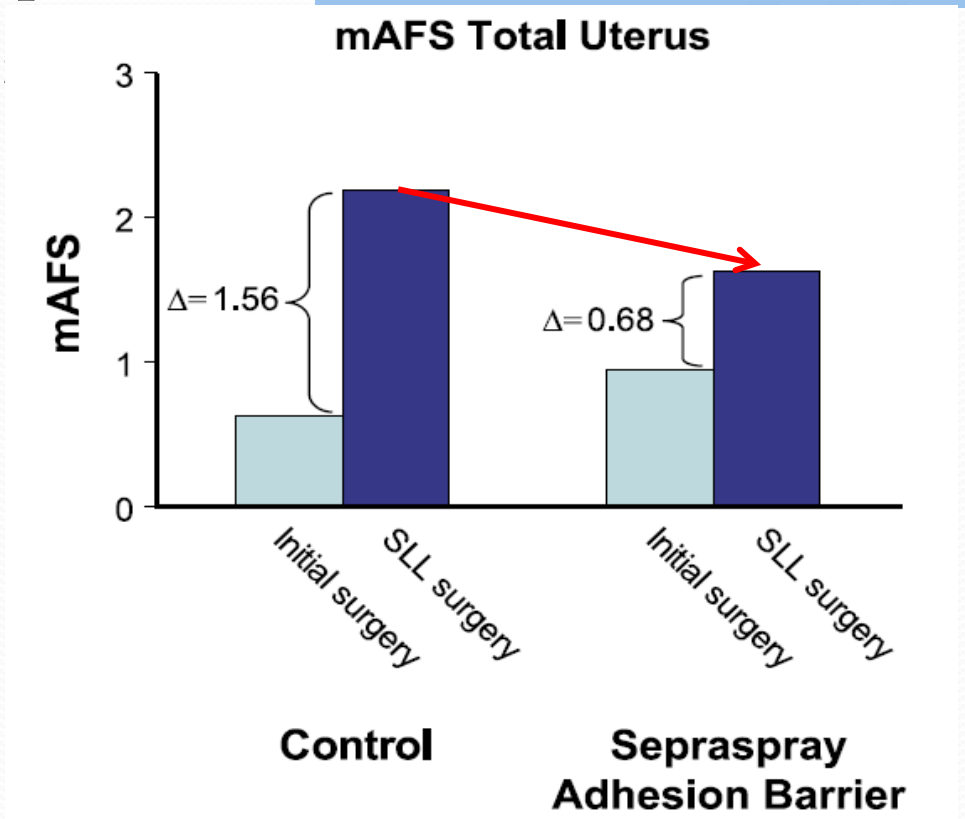
The patients were followed up according to the study protocol for 3 months. There were no unforeseen adverse events, possible adhesion-related complications, or nonspecific complications in either study arm. There was no significant difference in pelvic pain scores between PCT copolymer and icodextrin groups 3 months after surgery.

Kraemer, JMIG 2010

Sepraspray



- Hyaluronic acid + carboxymethyl cellulose (cfr.seprafilm)
- N=41



Fossum, Fertil Steril 2011

Spraygel

- Polyethylene-glycol
- N=64, ~80% laparoscopic myomectomy
- Second look in 40 patients

- Adhesions
  - **free of adhesion** **31,8 vs 11,1% (NS)**
  - Changes in incidence 0,64 vs 1,22 (p=0,035)
  - Changes in severity 0,6 vs 1,7 (p=0,001)

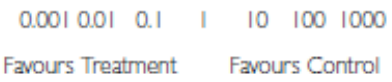
Spraygel ~ SprayShield™ Adhesion Barrier System

Mettler, Fertil Steril 2004

Spraygel: Cochrane (2006)

Analysis 10.1. Comparison 10 SprayGel versus no SprayGel, Outcome 1 proportion of adhesions at second-look laparoscopy.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Mettler 2004	15/22	16/18		100.0 %	0.27 [0.05, 1.50]
Total (95% CI)	**22**	**18**		**100.0 %**	**0.27 [0.05, 1.50]**
Total events: 15 (Treatment), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.50 (P = 0.13)					



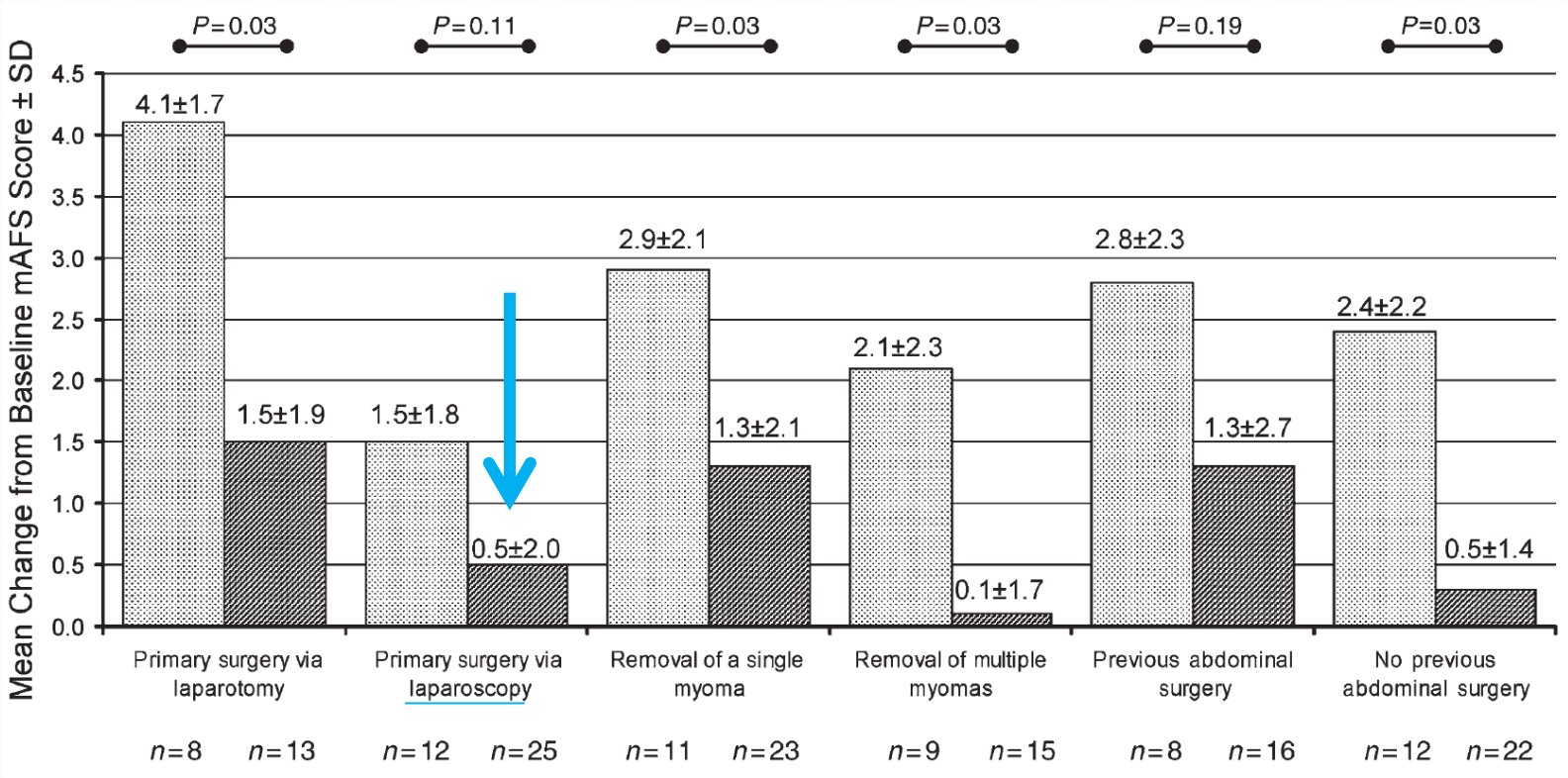
Coseal (spray)

- multicenter, randomized, single-blind study assessed the safety and efficacy of a resorbable hydrogel ('Hydrogel') for the reduction of post-operative adhesion formation following **myomectomy**
- Hydrogel was sprayed over all myomectomy suture lines and all surgically treated areas using a gas-assisted delivery system
- 58 had second look laparoscopy

Mettler, Hum Rep 2008

Coseal (spray)

- Hydrogel of polyethylene glycol
- N= 58 with second look



Mettler, Hum Rep 2008

Interceed

- Oxidized regenerated cellulose
- N= 546,

Adhesion characteristics of the 546 study participants.

laparoscopy

	~~Laparotomy plus AB~~			~~Laparotomy without AB~~		
	Group I (n = 136)	Group II (n = 138)	*P* value[a]	Group III (n = 135)	Group IV (n = 137)	*P* value[a]
Women with adhesions, n (%)	30 (22)	22 (15.9)	NS	38 (28.1)	31 (22.6)	NS
Filmy adhesions (avascular), n (%)	11 (8)	10 (7.2)	NS	10 (7.4)	8 (5.8)	NS
Organized adhesions (vascular and opaque), n (%)	9 (6.6)	7 (5)	NS	12 (8.8)	11 (8)	NS
Cohesive adhesions (serosa to serosa), n (%)	6 (4.4)	5 (3.6)	NS	16 (11.8)	12 (8.7)	NS

Note: AB = adhesion barrier.
[a] χ^2 test with 1 DF.

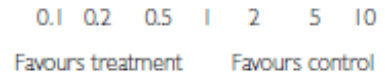
NS

Gynecare Interceed
Absorbable Adhesion Barrier

Tinelli, Fertil Steril 2011

Analysis 7.1. Comparison 7 FIBRIN SHEET VERSUS NO TREATMENT AT LAPAROSCOPIC MYOMECTOMY, Outcome 1 Incidence of adhesion per patient.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Takeuchi 2005	20/30	20/32		100.0 %	1.20 [0.42, 3.41]
Total (95% CI)	**30**	**32**		**100.0 %**	**1.20 [0.42, 3.41]**
Total events: 20 (Treatment), 20 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.73)					



Cochrane 2006

Risk factors of adnexal de novo adhesion calculated with logistic regression.

	Exp(β)	95% CI	*P* value
Size of largest myoma	1.015	1.002–1.027	.019
Total no. of myomas	1.128	1.064–1.196	.000
Adhesion-preventing agent*			
Fibrin glue	0.313	0.142–0.693	.004
→ Fibrin sheath	1.151	0.554–2.391	.706
Seprafilm	0.212	0.105–0.429	.000
Interceed	0.310	0.142–0.674	.003

n= 372, single surgeon

Takeuchi, Fertil Steril 2008

Hyaluronic acid at laparoscopy

Analysis 9.1. Comparison 9 Hyaluronic acid versus no hyaluronic acid, Outcome 1 proportion of adhesions at second- look laparoscopy.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Diamond 1998	119/137	103/108		25.1 %	0.32 [0.12, 0.89]
Johns 2001	12/131	33/134		49.2 %	0.31 [0.15, 0.63]
Lundorff 2001	4/38	6/39		8.8 %	0.65 [0.17, 2.50]
Pellicano 2003	5/18	14/18		16.8 %	0.11 [0.02, 0.50]
Total (95% CI)	**324**	**299**		**100.0 %**	**0.31 [0.19, 0.51]**

Total events: 140 (Treatment), 156 (Control)

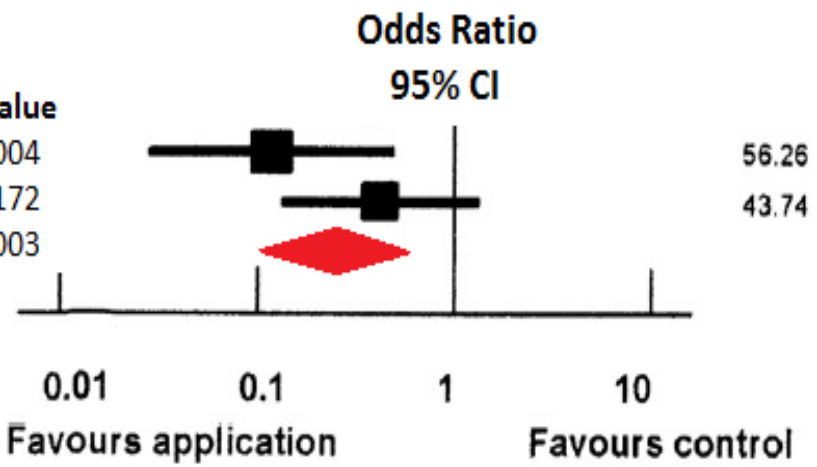
Heterogeneity: $Chi^2 = 2.94$, $df = 3$ ($P = 0.40$); $I^2 = 0.0\%$

Test for overall effect: $Z = 4.60$ ($P < 0.00001$)

Hyalobarrier gel

- Hyaluronic acid

	Patients with adhesion		Statistics for each study				
	Application	Control	Odds Ratio	Lower limit	Upper limit	Z-value	p-value
Pellicano	5/18	14/18	0.110	0.024	0.500	-2.855	0.004
Mais	8/21	13/22	0.426	0.125	1.449	-1.366	0.172
			0.248	0.098	0.628	-2.940	0.003



Mais, EJOGRB, 2012

Pellicano, '03-'05: Clinical Trial Design

- **36 infertile pts** with sympt **myomas** undergoing laparoscopic myomectomy
  - 18 patients randomized in Hyalobarrier® gel endo group
  - 18 patients in Control group (no anti-adhesion treatment)

- Procedure
  - Hyalobarrier® gel endo applied on the injured uterine surface, after removal of the myoma
  - Laparoscopic second-look 60-90 days after surgery
  - Follow-up at 6 and 12 months

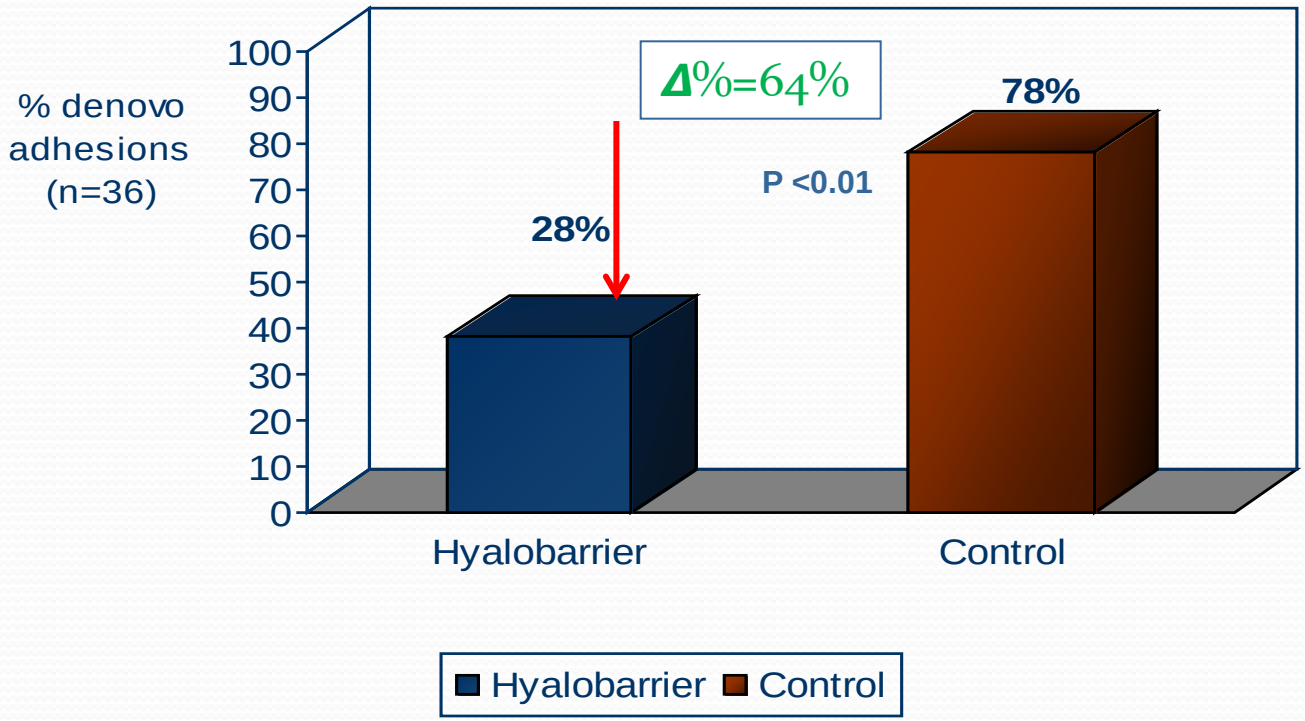
- Main outcomes
  - Incidence of **adhesions**
  - **Pregnancy rate** at 6 and 12 months

Pellicano M, Fertil Steril. 2003 Aug;80(2):441-4 ; Pellicano M., Fertil Steril. 2005 Feb;83(2):498-500

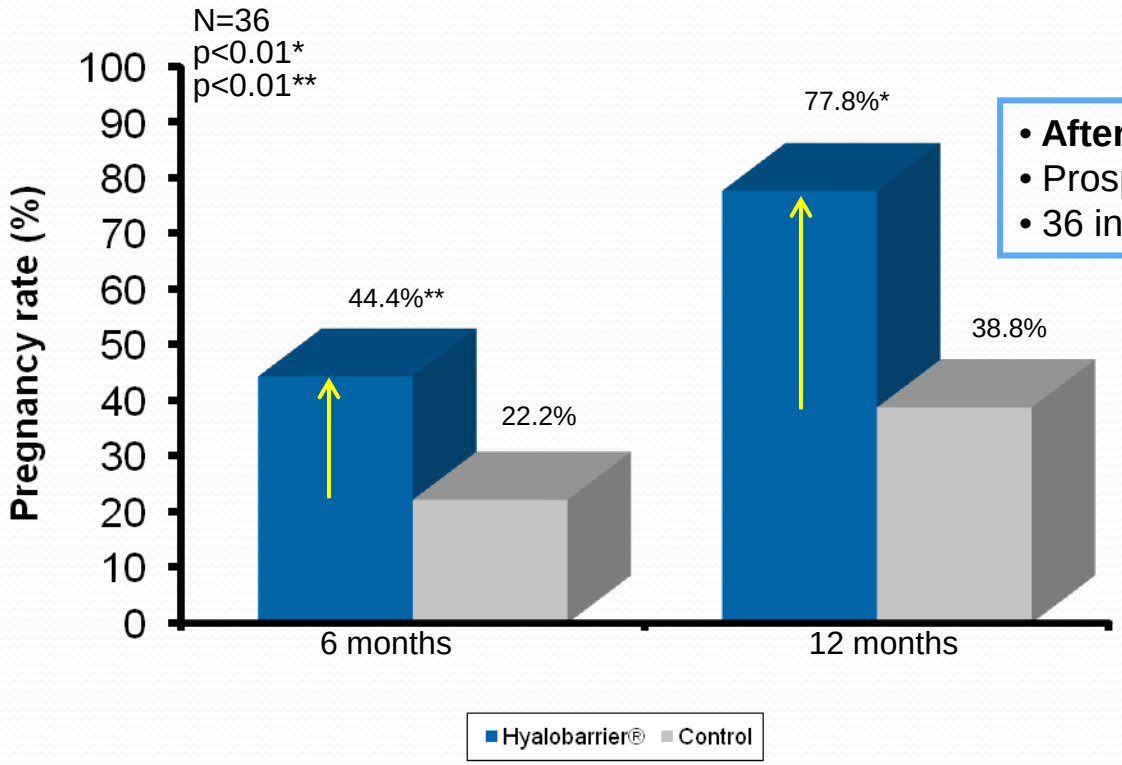
Hyalobarrier GEL | GEL ENDO

Results (Pellicano M., 2003)

Significant reduction in the incidence of adhesions



Results (Pellicano M., 2005)



- **After Laparoscopic Myomectomy**
- Prospective, randomised, controlled trial
- 36 infertile patients

Statistically significant difference between the 2 groups with respect to pregnancy rate at follow-up after 6 and 12 months.

Pellicano M et al., *Reproductive outcome after autocrosslinked hyaluronic acid gel application in infertile patients who underwent laparoscopic myomectomy.* Fertil Steril 2005 Feb; 83[2]: 498-500.

Hyalobarrier GEL | GEL ENDO

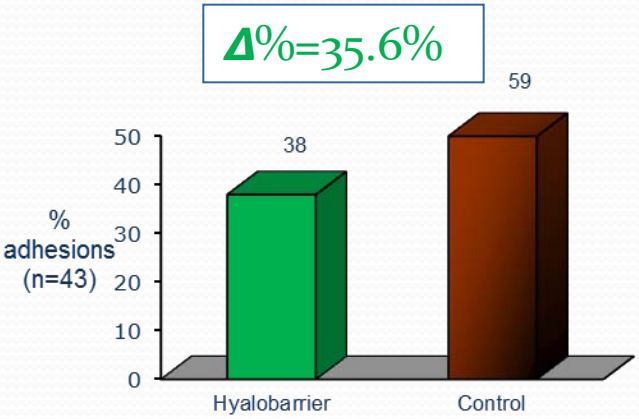
Mais V, 2006: clinical trial design

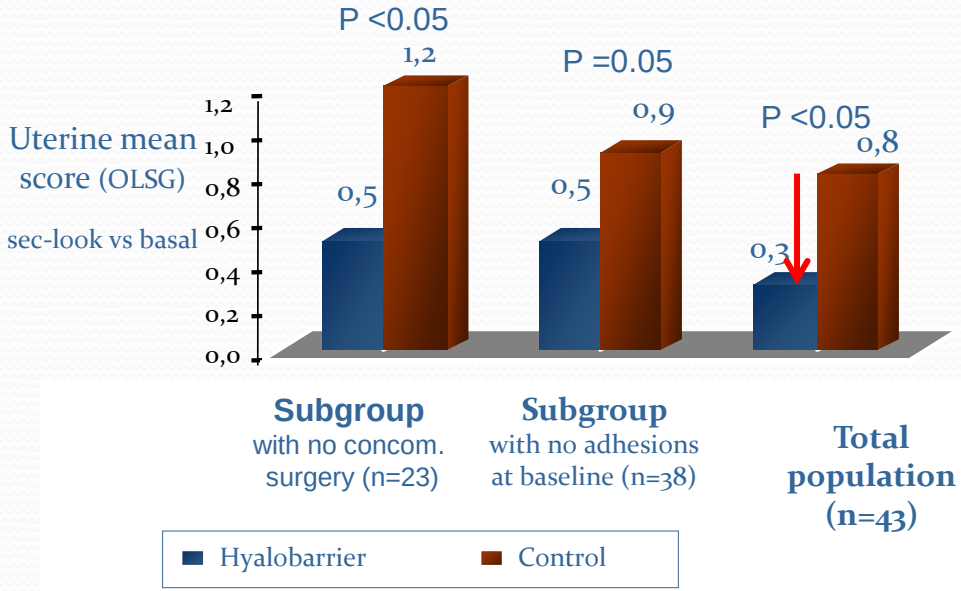
- 52 patients undergoing laparoscopic myomectomy
  - 26 patients randomized in Hyalobarrier® gel endo group
  - 26 patients in Control group (no anti-adhesion treatment)
- Procedure
  - Hyalobarrier® gel endo applied on all uterine incisions, after removal of the myoma
  - Blind laparoscopic second-look 90 days after surgery
- Main outcomes
  - Incidence and severity of adhesions

Hyalobarrier GEL | GEL ENDO

Results (Mais V., 2006)

Reduction in the incidence of adhesions



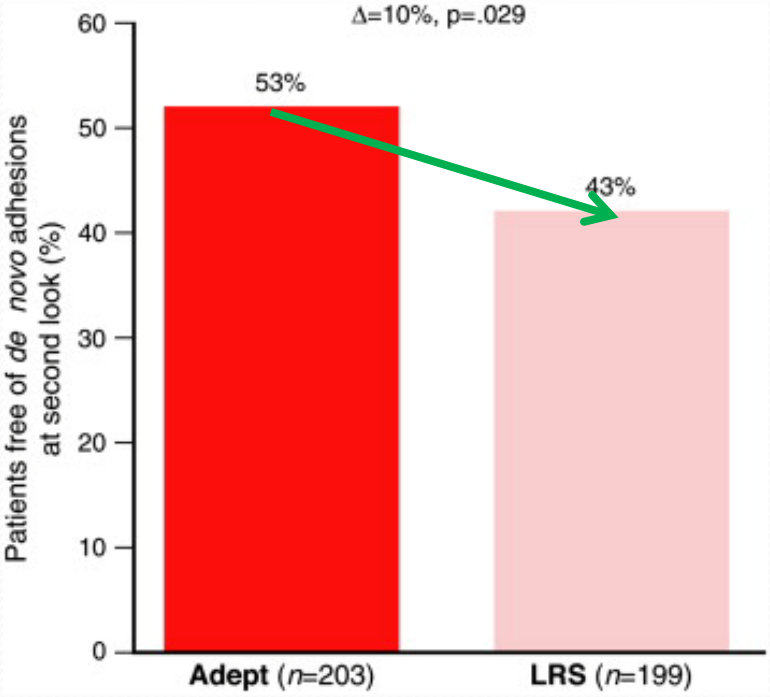


Reduction in the severity of adhesions

Hyalobarrier GEL | GEL ENDO

Barriers: Adept®

- ARIEL:"Adept® Registry for Clinical Evaluation"
  - 30.6% adverse events at laparotomy vs 6.7% at L'scopie
  - Mostly infectious events (4.2% - 3.4%)
- Adhesieprevention
  - RCT (n=402)
  - Free of de novo adhesions



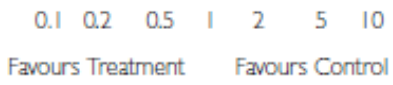
Ann R Coll Surg Engl 2006 Jyl;88(4):375-82

Brown et al. Fert Ster 2007

Icodextrin

Analysis 11.1. Comparison 11 Icodextrin versus no icodextrin, Outcome 1 proportion of adhesions at second look laparoscopy.

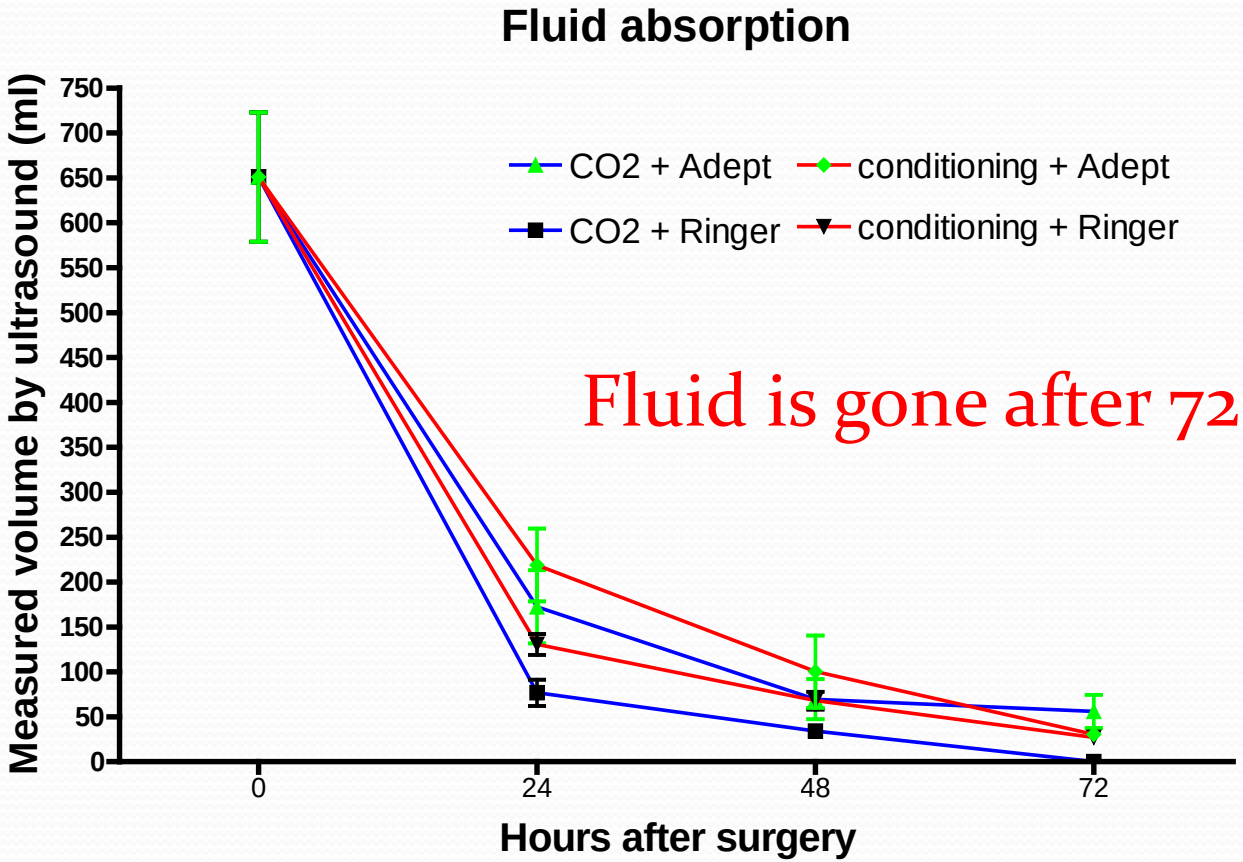
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
diZerega 2002	18/27	21/26		100.0 %	0.48 [0.13, 1.68]
Total (95% CI)	**27**	**26**		**100.0 %**	**0.48 [0.13, 1.68]**
Total events: 18 (Treatment), 21 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.15 (P = 0.25)					



No significant effect

Barriers: Adept®

- Instillation of 1 liter fluid (Ringer or Adept®)



Fluid is gone after 72 hours

Verguts J. Corona R, et al. manuscript prepared

Take Home Messages

Take Home messages

- No barrier, gas,… can make up for bad surgery

- Importance
  - Bleeding
  - Gas
  - Rinsing
  - Manipulation
  - Local trauma: barrier
  - Dexamethasone

Prevention

- PRIMARY
  - Laparoscopy, short duration
  - Alter the gas: N_2O + oxygen (conditioning)
  - Minimal manipulation of organs
  - Rinsing with Ringer + Heparine

- SECUNDARY
  - Use a barrier (Hyalobarrier or other)
  - Transplant mesothelial cells
  - Phospholipids, growth factors,…

Thank you