



Adhesion prevention in Reproductive Surgery

Special Interest Group Reproductive Surgery

7

3 July 2011
Stockholm, Sweden



Adhesion prevention in reproductive surgery

**Stockholm, Sweden
3 July 2011**

**Organised by
Special Interest Group Reproductive Surgery**

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Course coordinators

Marco Gergolet, Vassilios Tanos, Rudi Campo, Stephan Gordts

Target audience

Specialist gynaecologist, particularly those, involving in reproductive and endoscopic surgery

Scientific programme

| | |
|---------------|---|
| 09.00 - 09.30 | Pathophysiology of adhesion formation – Timur Gürgan (Turkey) |
| 09.30 - 09.45 | Discussion |
| 09.45 - 10.15 | Adhesion prevention in a laparoscopic mouse model – Maria Mercedes Binda (Belgium) |
| 10.15 - 10.30 | Discussion |
| 10.30 - 11.00 | Coffee break |
| 11.00 - 11.30 | Adhesions and reproduction – Stephan Gordts (Belgium) |
| 11.30 - 11.45 | Discussion |
| 11.45 - 12.15 | Adhesion prophylaxis in clinical routine: lessons learned from experimental models to clinical applications – Luciano Nardo (United Kingdom) |
| 12.15 - 12.30 | Discussion |
| 12.30 - 13.30 | Lunch |
| 13.30 – 13.50 | Postoperative intra uterine adhesions: why? – Pietro Gambadauro (Sweden) |
| 13.50 – 14.15 | Hysteroscopic treatment of Asherman syndrome – Tin-Chiu Li (United Kingdom) |
| 14.15 – 14.45 | Prevention of postoperative intra uterine adhesions – Rudi Campo (Belgium) |
| 14.45 – 15.00 | Discussion |
| 15.00 - 15.30 | Coffee break |
| 15.30 - 16.00 | Adhesion formation after ovarian drilling comparison of laparoscopy and fertiloscopy – Antoine Watrelot (France) |
| 16.15 - 16.45 | No postoperative adhesions anymore: fiction or reality? – Philippe Koninckx (Belgium) |
| 16.45 - 17.00 | Discussion and closing remarks – Marco Gergolet (Italy) |



ESHRE – European Society of Human Reproduction and Embryology

What is ESHRE?

ESHRE was founded in 1985 and its **Mission Statement** is to:

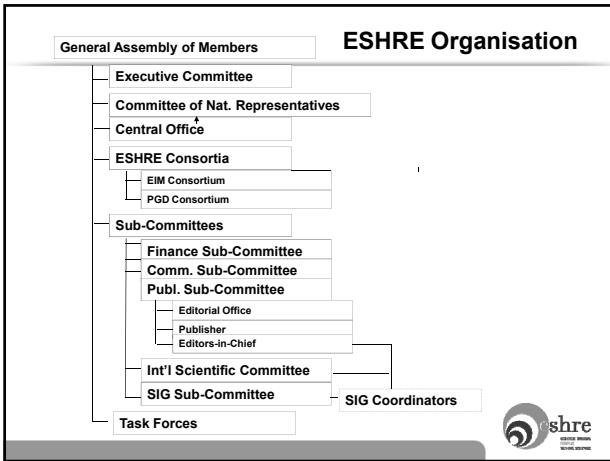
- promote interest in, and understanding of, reproductive science
- facilitate research and dissemination of research findings in human reproduction and embryology to the general public, scientists, clinicians and patient associations.
- inform policy makers in Europe
- promote improvements in clinical practice through educational activities
- develop and maintain data registries
- implement methods to improve safety and quality assurance



Executive Committee 2009/2011


| | | |
|----------------|---------------------------------|----------------|
| Chairman | • Luca Gianaroli | Italy |
| Chairman Elect | • Anna Veiga | Spain |
| Past Chairman | • Joep Geraedts | Netherlands |
| | • Jean François Guérin | France |
| | • Timur Gürgan | Turkey |
| | • Ursula Eichenlaub-Ritter | Germany |
| | • Antonis Makrigiannakis | Greece |
| | • Miodrag Stojkovic | Serbia |
| | • Anne-Maria Suikkari | Finland |
| | • Carlos Plancha | Portugal |
| | • Françoise Shenfield | United Kingdom |
| | • Etienne Van den Abbeel | Belgium |
| | • Jolieneke Schoonenberg-Pomper | Netherlands |
| | • Veljko Vlaisavljevic | Slovenia |
| | • Søren Ziebe | Denmark |






ESHRE Journals



Human Reproduction with impact factor 3.859



Human Reproduction Update with impact factor 7.042



Molecular Human Reproduction with impact factor 3.005


Campus Activities and Data Collection

Campus / Workshops

- Meetings are organised across Europe by Special Interest Groups and Task Forces
- Visit www.eshre.eu under CALENDAR

Data collection and monitoring

- European IVF Monitoring Group data collection
- PGD Consortium data collection



ESHRE Activities

- Embryology Certification
- Guidelines
- Position papers
- News magazine “Focus on Reproduction”



ESHRE Clinical Embryologist Certification Exam Page 1 of 16
 28 June 2009, Amsterdam
Clinical Embryology Certification Examination

1. Which of the following statements is true?
 Numbers:







- a. A centriole from the sperm forms the zona.
- b. The zygote loses the mitochondria.
- c. Polypermic oocytes divide to form two pronuclei.
- d. Major activation of the human embryo occurs at fertilisation.

ESHRE Pages
 Revised guidelines for good practice in IVF laboratories

14. Cristina Magli, Shireen Yasmin Akhtar, Soren Lunde, Neelke Doornik, Zeynep Yildirim and Liisa Giustolisi for Committee of the Special Interest Group on Assisted Reproduction
 Contact: Dr. Frank Oels, Editor, ESHRE Publications, 200, Avenue de la Republique, Laarbeek 200, 2015 Brussels, Belgium. E-mail: frank@eshre.org



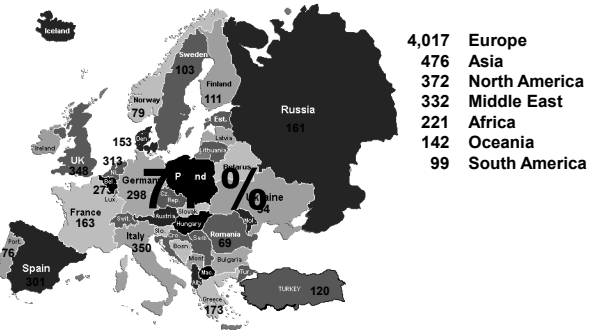
ESHRE COMMUNITY

-  RSS feeds for news in reproductive medicine
-  Since launch 12/2009: **1,360 Fans**
-  Since launch 12/2009: **190 followers**
 (journalists, scientific organisations, patient societies, governmental bodies)
-  Retweets to MHR
-  

[Find a member](#)



ESHRE Membership (1/3)



TOTAL MEMBERSHIP*: 5 659 members



ESHRE Membership (2/3)

| | 1 yr | 3 yrs |
|---------------------|------|-------|
| Ordinary Member | € 60 | € 180 |
| Paramedical Member* | € 30 | € 90 |
| Student Member** | € 30 | N.A. |

*Paramedical membership applies to support personnel working in a routine environment such as nurses and lab technicians.
 **Student membership applies to undergraduate, graduate and medical students, residents and post-doctoral research trainees.



ESHRE Membership – Benefits (3/3)

1) Reduced registration fees for all ESHRE activities:

| | | | |
|----------------|-----------------------|-------|---------|
| Annual Meeting | Ordinary | € 480 | (€ 720) |
| | Students/Paramedicals | € 240 | (€ 360) |
| Workshops* | All members | €150 | (€ 250) |

2) Reduced subscription fees to all ESHRE journals – e.g. for Human Reproduction €191 (€ 573!)

3) ESHRE monthly e-newsletter

4) News Magazine "Focus on Reproduction" (3 issues p.a.)

5) Active participation in the Society's policy-making

*workshop fees may vary



Special Interest Groups (SIGs)

The SIGs reflect the scientific interests of the Society's membership and bring together members of the Society in sub-fields of common interest

| | |
|-----------------------------|----------------------------|
| Andrology | Psychology & Counselling |
| Early Pregnancy | Reproductive Genetics |
| Embryology | Reproductive Surgery |
| Endometriosis / Endometrium | Stem Cells |
| Ethics & Law | Reproductive Endocrinology |
| Safety & Quality in ART | |



Task Forces

A task force is a unit established to work on a single defined task / activity

- Fertility Preservation in Severe Diseases
- Developing Countries and Infertility
- Cross Border Reproductive Care
- Reproduction and Society
- Basic Reproductive Science
- Fertility and Viral Diseases
- Management of Infertility Units
- PGS
- EU Tissues and Cells Directive



ESHRE – Annual Meeting

- One of the most important events in reproductive science
- Steady increase in terms of attendance and of scientific recognition

Track record:

ESHRE 2010 – Rome: 9,204 participants
ESHRE 2009 – Amsterdam: 8,055 participants
ESHRE 2008 – Barcelona: 7,559 participants

Future meetings:

ESHRE 2011 – Stockholm, 3-6 July 2011
ESHRE 2012 – Istanbul, 1-4 July 2012



ESHRE 2011, Stockholm, Sweden

When: 3 - 6 July 2011

Where: Stockholmsmässan,
Mäsvägen 1, Älvsjö, Sweden
www.stockholmsmassan.se



Chair of conference: Kersti Lundin

Hotel and Travel:
MCI - Stockholm Office
Phone: +46 (0)8 54651500
E-mail: eshre@mci-group.com



For updates visit www.eshre.eu



ESHRE 2011, Stockholm

Keynote Lectures

Aneuploidy in humans: what we know and we wish we knew – Terry Hassold (USA)

Historical Lecture

A brave new world with a brave old humankind; quo vadimus – E. Diczfalusy (SE)

MHR Symposium – The paternal genome

Sperm chromatin packaging – B. Robaire (CDN)

The human sperm epigenome – B. Cairns (USA)



ESHRE 2011, Stockholm: Debates

This house believes that obese women should not receive treatment until they have lost weight

- Yes: Mark Hamilton (UK)
- No: Guido de Wert (NL) - TBC

Paramedical invited session: Should we pay donors?

- Yes: Herman Tournaye (BE)
- No: Laura Witjens (UK)



Annual Meeting – Pre-Congress Courses

- PCC 1: The challenges of embryo transfer (Paramedical Group)
- PCC 2: The blastocyst: perpetuating life (SIG Embryology and SIG Stem Cells)
- PCC 3: From genes to gestation
(SIG Early Pregnancy and SIG Reproductive Genetics)
- PCC 4: Lifestyle and male reproduction (SIG Andrology)
- PCC 5: Ovarian ageing (SIG Reproductive Endocrinology)
- PCC 6: The impact of the reproductive tract environment on implantation success (SIG Endometriosis/Endometrium)
- PCC 7: Adhesion prevention in reproductive surgery
(SIG Reproductive Surgery)



Annual Meeting – Pre-congress Courses

- PCC 8: Theory and practice update in third party reproduction (SIG Psychology and Counselling)
- PCC 9: Ethical aspects of non-invasive prenatal diagnosis (SIG Ethics & Law)
- PCC 10: Patient-centered fertility services (SIG SQUART)
- PCC 11: Clinical management planning for fertility preservation in female cancer patients (TF Basic Science and TF Preservation in Severe Disease in collaboration with the US OncoFertility Consortium)
- PCC 12: Opportunities for research in female germ cell biology (TF Basic Science)



Annual Meeting – Pre-congress courses

- PCC 13: Assisted reproduction in couples with HIV (TF Fertility and Viral Diseases)
- PCC 14: Prevention of infertility – from preconception to post-menopause (TF Reproduction and Society)
- PCC 15: Hot topics in male and female reproduction (ASRM exchange course)
- PCC 16: Academic Authorship programme (Associate Editors ESHRE journals)
- PCC 17: Science and the media, an introduction to effective communication with the media (Communications SubCommittee ESHRE)



Certificate of attendance

- 1/ Please fill out the evaluation form during the campus
- 2/ After the campus you can retrieve your certificate of attendance at www.eshre.eu
- 3/ You need to enter the results of the evaluation form online
- 4/ Once the results are entered, you can print the certificate of attendance from the ESHRE website
- 5/ After the campus you will receive an email from ESHRE with the instructions
- 6/ You will have TWO WEEKS to print your certificate of attendance



Contact



ESHRE Central Office
Tel: +32 (0)2 269 09 69
info@eshre.eu / www.eshre.eu

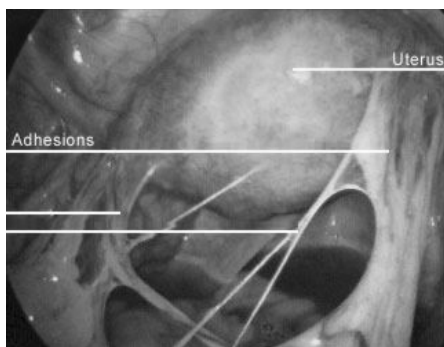


Pathophysiology of adhesion formation

Timur Gurgan, M.D
Professor, Hacettepe University, Dept of Ob&Gyn,
Reproductive Endocrinology and IVF Unit
Ankara, Turkey

Adhesion

- **Definition:** Non-anatomic connections of fibrous tissue between normal peritoneal surfaces
- **Classification:**
 - Type 1 (de novo) → newly formed
 - Type 2 (re-formed) → develops at the sites of previous adhesiolysis



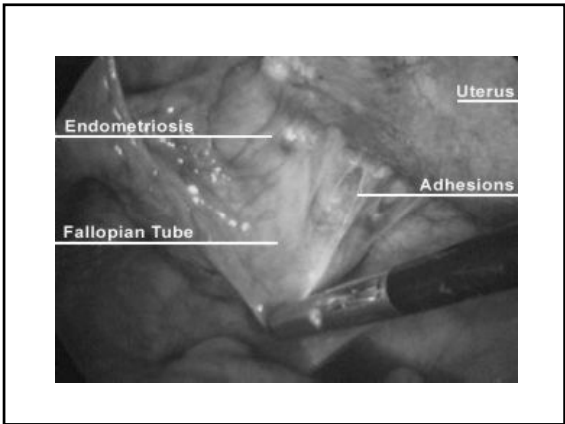


Table 1 Classification of Postoperative Adhesion Development

| | |
|---------------|--|
| Type 1 | De novo adhesion formation; development of adhesions at sites that did not have adhesion initially |
| A | No operative procedure at site of adhesion formation |
| B | Operative procedure performed at site of adhesion formation |
| Type 2 | Adhesion re-formation; redevelopment of adhesions at sites at which adhesiolysis was performed |
| A | No operative procedure at site of adhesion re-formation (other than adhesiolysis) |
| B | Operative procedure performed at site of adhesion re-formation (in addition to adhesiolysis) |

Source: Diamond MP, Nezhat F. Adhesions after resection of ovarian endometriomas. Fertil Steril 1993;59:934-935.

Cause of adhesion formation

- Adhesions develop after an injury to the normal peritoneal tissue. This injury can result from surgery, trauma, inflammation, infection, or foreign body placement in the peritoneal cavity.

Key factors in adhesion formation

- Adhesions develop as a response to hypoxia whereby the body tries to reestablish oxygen and nutrient supply to tissues that have been injured by surgery or previous pathology
- Infection mediated cascade inflammatory by-products may play a role in adhesion formation
- Tissue injury results in bleeding and leakage of lymphatic fluid from transected vessels, a process that is accentuated by concomitant histamine release

Key factors in adhesion formation

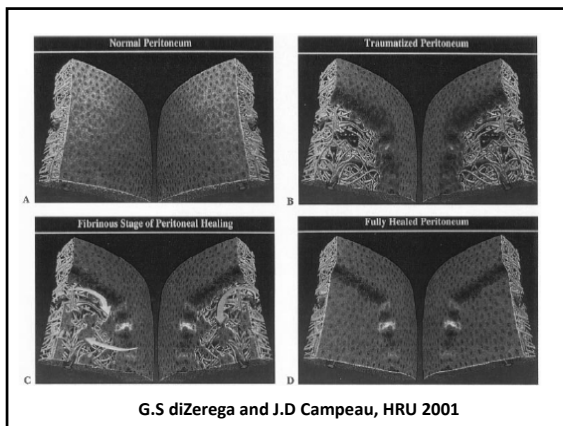
- Accumulation of red and white blood cells, platelets, clotting and growth factors, and cytokines which coagulate to form a fibrin clot is necessary for reconstitution of the injured tissue
- Formation of fibrin matrix in the presence of suppressed fibrinolysis

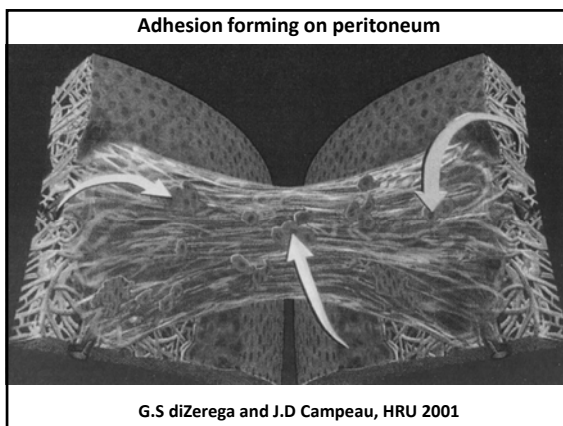
Normal healing process

- During normal healing, the fibrinous mass is removed by fibrinolysis
- Extracellular matrix have been achieved
- Fibroblast growth and deposition occurs
- All these steps allows tissue to heal without inappropriate attachment to other tissues


Adhesion formation

- Injury to the normal mesothelial cells overlaying the peritoneal surface starts the healing process
- Disruption of stromal mast cells cause to release of vasoactive substances such as histamines and kinins
- Increase in the vascular permeability contributes
- Collection of fibrin-rich exudate occurs
- Exudate covers the injured area.





Two processes occur simultaneously

 the fibrin polymers in this exudate interact with fibronectin to form the fibrin gel matrix, which consequently produces fibrin bands between the injured areas

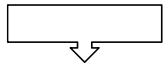
AND

 fibrinolysis

Healing process ± Adhesion formation

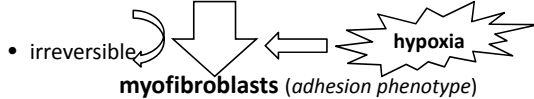
- Fibrinolysis dominates at sites where healing occurs without adhesions
- If fibrinolysis is impaired, this imbalance may result in the persistence of the fibrinous mass. Subsequently, proliferating fibroblasts invade this area and deposit extracellular matrix material including collagen that contributes to the formation of adhesion

Ischemia



- most important insult that leads to adhesion development

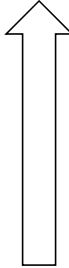
fibroblasts in the adhesion tissues



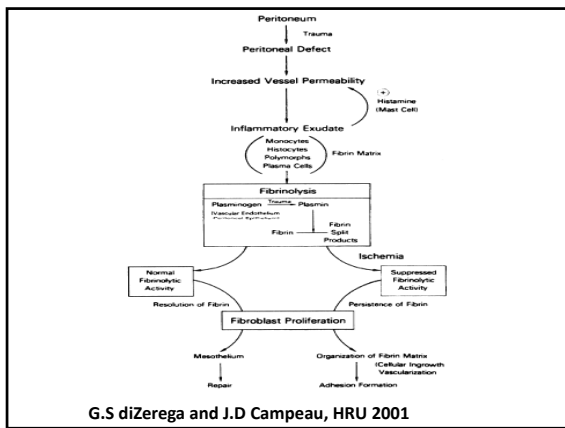
Saed and Diamond, F&S 2002 – Saed and Diamond JAAGL 2004

Adhesion fibroblast(myofibroblast)


- basal mRNA levels for collagen I
- fibronectin
- matrix metalloproteinase-1 (MMP-1)
- tissue inhibitor of metalloproteinase-1 (TIMP-1)
- transforming growth factor (TGF)-b1
- TGF-b2
- cyclooxygenase-2 (COX-2)
- interleukin (IL)-10
- protein nitration



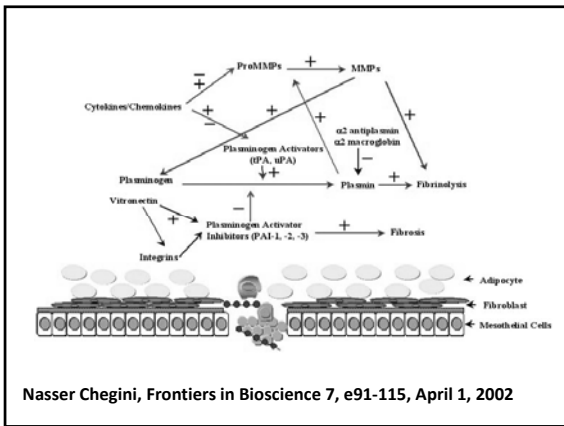
Saed and Diamond, F&S 2003 – Idell S et al, Am J Physiology 1992 – Saed et al, HR 2006

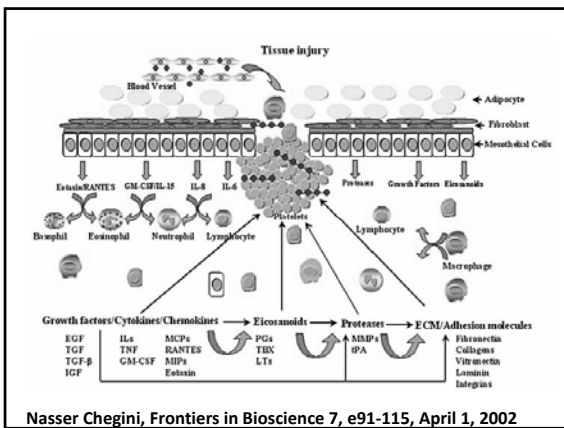


Other factors in adhesion formation

- apoptosis rate  in adhesion type fibroblasts
- Apoptosis may be inhibited by hypoxia

Saed and Diamond, F&S 2003 – Idell S et al, Am J Physiology 1992 – Saed et al, HR 2006





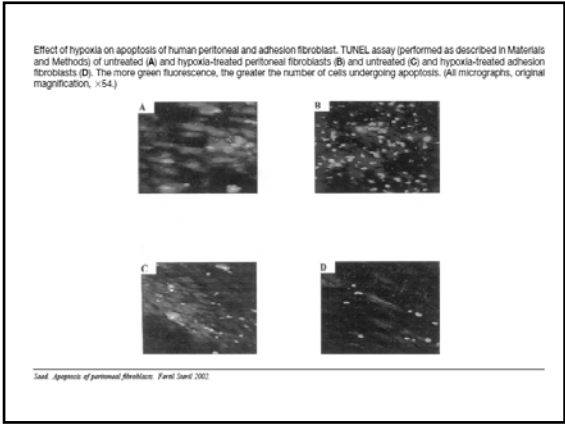
FERILITY AND FERTILITY*
 ISSN: 1525-2025 (print), 1525-2033 (online)
 Copyright © 2002 American Society for Reproductive Medicine
 Published by Elsevier Science Inc.
 Printed in and from page 6, U.S.A.

Apoptosis and proliferation of human peritoneal fibroblasts in response to hypoxia

Ghassan M. Saad, Ph.D., and Michael P. Diamond, M.D.
 Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, and the C. S. Mott Center for Human Growth and Development, Wayne State University, Detroit, Michigan

Result(s): Compared with fibroblasts from normal peritoneum, fibroblasts from adhesions had significant complementary decreases in apoptosis and an increase in proliferation. In response to hypoxia, the Bcl-2-bax mRNA ratio was significantly higher in fibroblasts from adhesions as compared with fibroblasts from normal peritoneum. The degree of apoptosis induced by hypoxia correlated with the increase in the bcl-2-bax ratio in fibroblasts derived from both normal peritoneum and adhesions.

Conclusion(s): Hypoxia induces proliferation while inhibiting apoptosis in fibroblasts from adhesion, thereby creating a phenotype that would favor adhesion development. (*Fertil Steril*® 2002;78:137-43. ©2002 by American Society for Reproductive Medicine.)



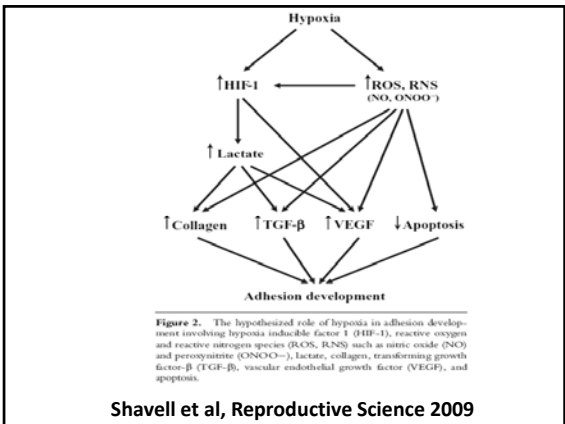
REVIEW

Cellular Metabolism: Contribution to Postoperative Adhesion Development

Valerie I. Shavell, MD, Ghassan M. Saed, PhD, and Michael P. Diamond, MD

- Contributions of intermediary metabolism to peritoneal healing
- Possible role in mediating postoperative adhesion development
- Hypoxia is a key factor in intracellular mechanisms (promotion of anaerobic glycolysis and glucose uptake by HIFs, the activation of collagen synthesis and angiogenesis by lactate and NO, the inhibition of apoptosis by peroxynitrite, the stimulation of collagen production and the inhibition of apoptosis by IGFs)
- Intermediary metabolism's direct role in cellular mechanisms leading to wound repair in the presence or absence of adhesions

Reproductive Science, 2009



Importance of intrinsic protective fibrinolytic activity in adhesion formation

- tPA and PAI-1
- the ratio between tPA and PAI-1 is a better marker of fibrinolytic potential than just using levels individually
- The tPA/PAI-1 ratio has been shown to be 80% higher in normal peritoneal fibroblasts than in adhesion fibroblasts under hypoxic conditions
- This ratio significantly decreases in normal fibroblasts (90%)
- more exaggerated decrease observed in adhesion fibroblasts (98%)

Saed and Diamond, F&S 2004 - Alpay et al, Semin Reprod Med, 2008

Healing process extracellular matrix remodeling

- Hypoxia has been shown to inhibit MMP-1 and MMP-9 and augment TIMP-1 expression
- ↓ MMP:TIMP ratio during hypoxia (98%) may favor the increase in extracellular matrix production and the decrease in turnover and degradation that eventually may lead to tissue fibrosis and adhesion development

Sandell LJ, Connect Tissue Res 1996 – Diamond et al, F&S 2004 - Saed et al, J S Gyn Invest 2000

postoperative adhesions development regulation of inflammatory and angiogenesis step

- In adhesion fibroblasts, the expression of COX-2 is significantly increased compared with that of the normal fibroblasts
- COX-2 enzyme has an important role in the regulation of inflammatory and angiogenesis steps of postoperative adhesions development
- Hypoxia enhances the level of COX-2 expression in normal fibroblasts whereas there is no change in adhesion fibroblasts

Saed et al, F&S 2005

nitric oxide in adhesion formation

- Involved in the formation and maintenance of adhesions
- potent vasodilator
- Inhibitor of thrombus formation
- Wound healing (analogous in many respects to adhesion formation) \Rightarrow associated with increased NO levels

Lamas et al, Proc Natl Acad Sci, 1992 – Schaffer et al, J Surg Res, 1996 and 1997

Infect Dis Obstet Gynecol 2001;9:113-116

Adhesion development and the expression of endothelial nitric oxide synthase

David M. Svinarich¹, Fadi M. Zaher¹, Lena Holmdahl¹, Nasser Chegini², Bernard Gonik¹ and Michael P. Diamond¹, for the PHAMUS group

This pilot study demonstrates that adhesions transcriptionally express eNOS. Furthermore, eNOS mRNA levels are substantially greater in adhesions than in either skin, subcutaneous tissue or normal peritoneum. This suggests that NO may be an important modulator of adhesion formation and maintenance

Conclusion

- Peritoneal adhesions are the leading cause of pelvic pain, bowel obstruction and infertility
- The mechanisms underlying the predisposition to adhesion formation are completely unknown
- Understanding of adhesion formation at the molecular level is essential
- These informations will help to prevent adhesion



Adhesion prevention in a laparoscopic mouse model

M. Mercedes Binda, Ph.D.

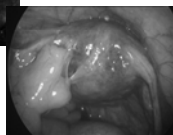
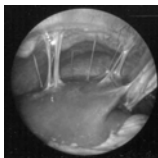
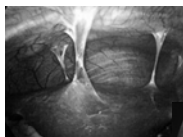
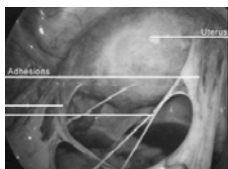
Associated Researcher

Department of Gynaecology and Obstetrics, University Hospital Gasthuisberg, Catholic University of Leuven, Leuven, Belgium

Learning objectives

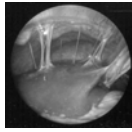
- ▶ Adhesions: definition, clinical problem and incidence, type of adhesions.
- ▶ Pathogenesis: traditional model.
- ▶ Laparoscopic mouse model: set up, induction of adhesions and scoring system.
- ▶ CO₂ pneumoperitoneum as a cofactor in adhesion formation: hypoxia, hyperoxia, desiccation and cooling.
- ▶ Peritoneal cavity as a cofactor in adhesion formation: inflammation and manipulation
- ▶ Conditioning of the abdominal cavity and adhesion prevention products
- ▶ Conclusions: New concept in adhesion prevention

Intraperitoneal Adhesions



Abnormal fibrous connections between surfaces in the abdominal cavity.

Important Clinical Problem



Associated morbidity: intestinal obstruction, chronic pelvic pain, female infertility

Difficulties at the time of reoperation: difficult access, organs injury, bleeding.

Large utilisation of healthcare resources: increased operating, anaesthesia and recovery time, need of blood transfusion, and use of surgical material.

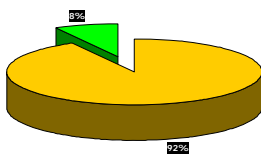
Huge economic impact: e.g. 1.3 billion US\$ per year in USA.

Incidence

Menzies D, Ellis H. Ann R Coll Surg Engl 1990

Patients without previous surgery

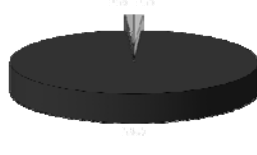
12/115: 10.4%



Post-inflammatory
 Congenital
 Post-operative

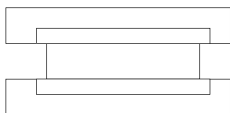
Patients with previous surgery

198/210: 94.3%

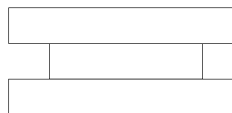


Postoperative adhesions

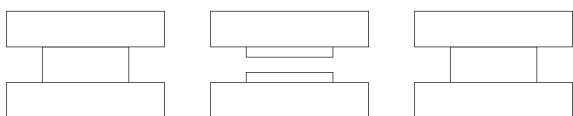
Adhesion formation



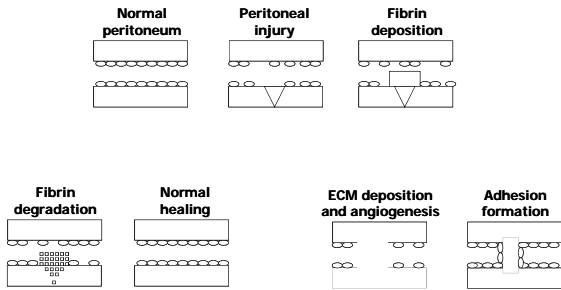
De novo adhesion formation



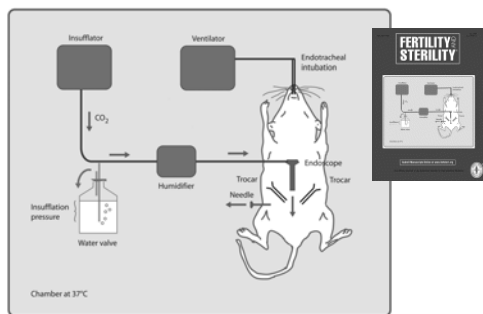
Adhesion reformation



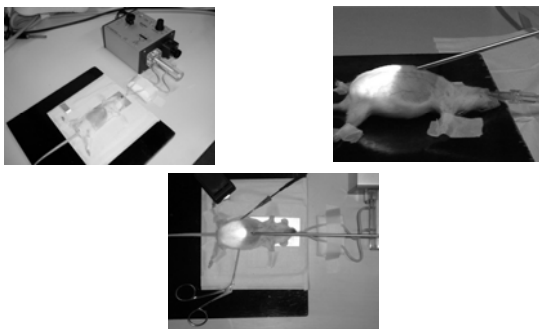
Pathogenesis: Traditional model: a local phenomenon



The laparoscopic mouse model Set up

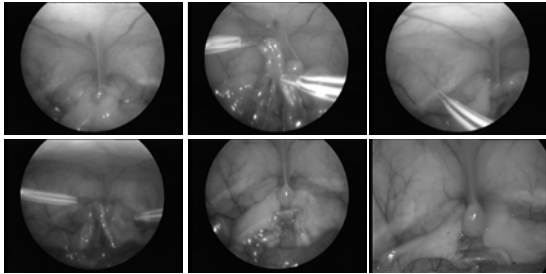


The laparoscopic mouse model Set up



The laparoscopic mouse model
Induction of adhesions

Standardised bipolar lesions in uterine horns and pelvic sidewalls during laparoscopy

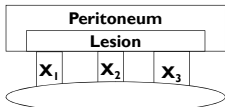


The laparoscopic mouse model
Scoring of adhesions

After 7 days, blindly, under microscopic vision, during laparotomy

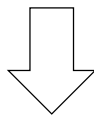
Quantitative scoring

$$\text{Adhesions (\%)} = \frac{\sum \text{length of the individual attachments}}{\text{Length of the lesion}}$$



- Qualitative scoring
- > Extent: 0 - 4
 - > Type: 0 - 3
 - > Tenacity: 0 - 3
 - > Total: 0 - 10

CO₂ pneumoperitoneum is a cofactor in adhesion formation (2001)

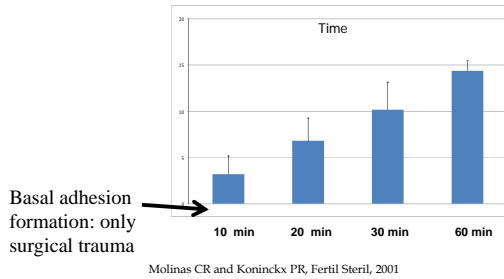


Peritoneal cavity as a cofactor in adhesion formation (2009)

CO₂ pneumoperitoneum is a cofactor in adhesion formation

1. Duration

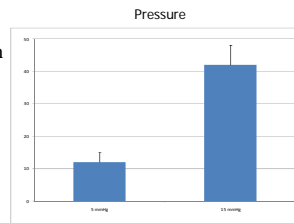
- Adhesions increase with duration of surgery



CO₂ pneumoperitoneum is a cofactor in adhesion formation

2. Pressure

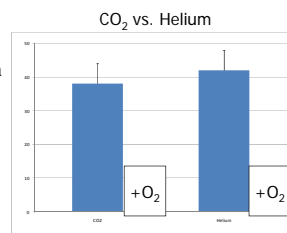
- Adhesions increase with insufflation pressure



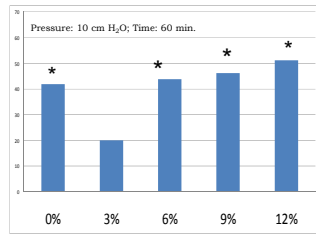
CO₂ pneumoperitoneum is a cofactor in adhesion formation

3. Type of insufflation gas

- Adhesions are similar with CO₂ and Helium pneumoperitoneum
- Adhesions decrease after addition of 3-4% oxygen



CO₂ pneumoperitoneum is a cofactor in adhesion formation
3.Type of insufflation gas

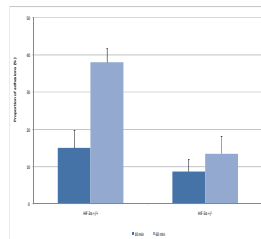


➤ Adhesions increase with the addition of more than 3% Oxygen to the pneumoperitoneum (Elkelani OA, Binda MM *et al.* Fert Steril 2004)

* P vs 3% <0.05, Wilcoxon

CO₂ pneumoperitoneum is a cofactor in adhesion formation
Hypothesis of mesothelial hypoxia

✓ Consistent with the absence of pneumoperitoneum-enhanced adhesion in mice knockout for HIFs, VEGF-A, VEGF-B, PIGF and PAI-1.

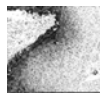


Molinas *et al.*, Fert Steril 2003
 Molinas *et al.*, Fert Steril 2003
 Molinas *et al.*, Fert Steril 2003

CO₂ pneumoperitoneum is a cofactor in adhesion formation
3.Type of insufflation gas: mesothelial hypoxia

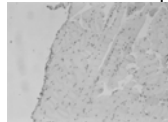
Unpublished observations

Hypoxyprobe™-1 Immunoperoxidase staining for hypoxia

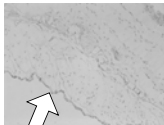


Ctrl (+)

Control without laparoscopy

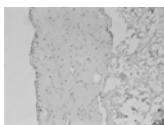


60 min CO₂ PP



Mesothelial Hypoxia

60 min +3%O₂ PP

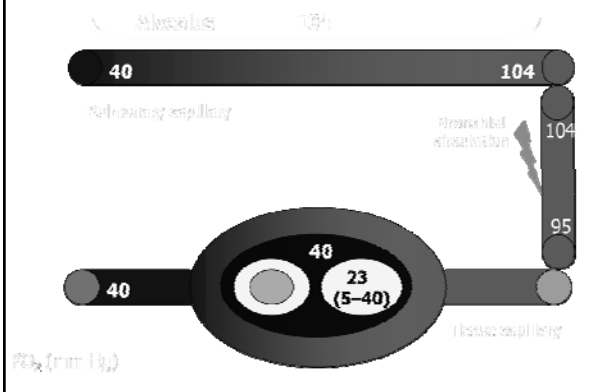


Why adding 3-4% Oxygen reduces adhesions?

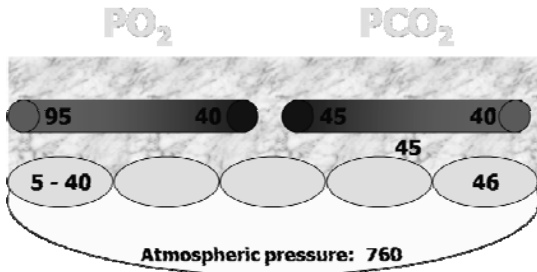
Partial pressures of respiratory gases

| | Atmospheric air | | Humidified air | | Alveolar air | |
|------------------|-----------------|-------|----------------|-------|--------------|-------|
| | PP (mm Hg) | % | PP (mm Hg) | % | PP (mm Hg) | % |
| N ₂ | 597.0 | 78.62 | 563.4 | 74.09 | 569.0 | 74.90 |
| O ₂ | 159.0 | 20.84 | 149.3 | 19.67 | 104.0 | 13.60 |
| CO ₂ | 0.3 | 0.04 | 0.3 | 0.04 | 40.0 | 5.30 |
| H ₂ O | 3.7 | 0.50 | 47.0 | 6.20 | 47.0 | 6.20 |
| Total | 760 mm Hg | | | | | |

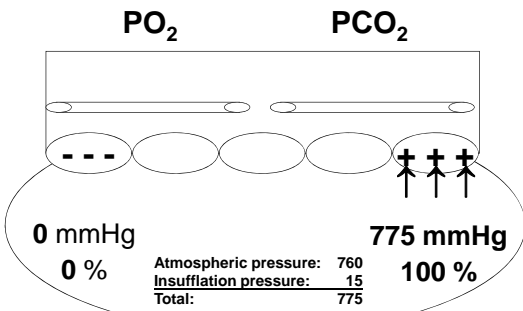
Transport of oxygen



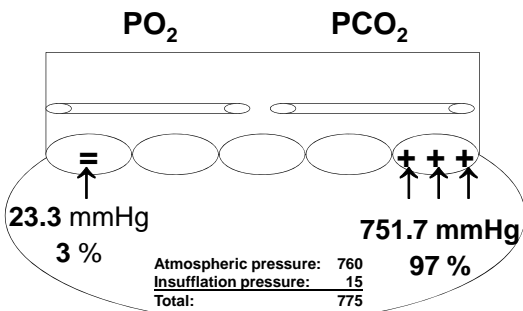
Normal conditions



Pneumoperitoneum with 100% CO₂

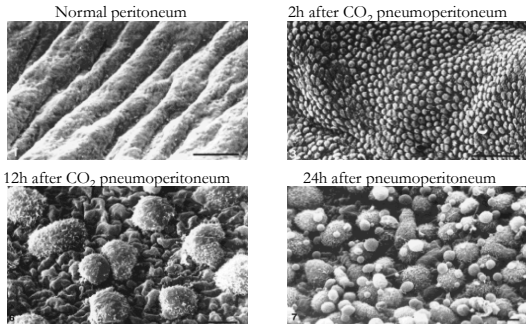


Pneumoperitoneum with 97% CO₂ + 3% O₂



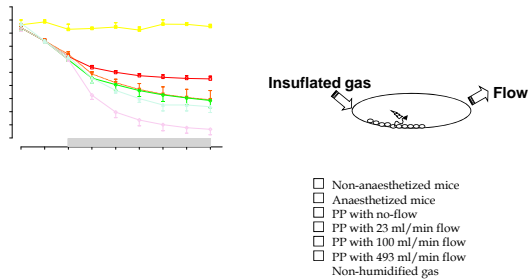
CO₂ pneumoperitoneum is a cofactor in adhesion formation

4. Dry insufflation gas produces desiccation

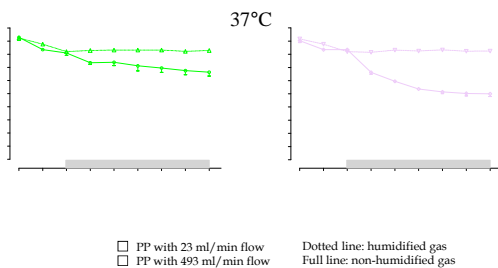


Volz J *et al.* Surg Endosc 1999.

Desiccation and temperature
Non-humidified pneumoperitoneum produces cooling

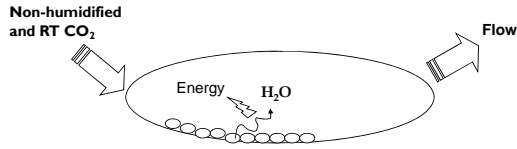


Desiccation and temperature
Cooling is avoid using humidified gas



Desiccation and cooling

Why dry gas produces cooling and desiccation?

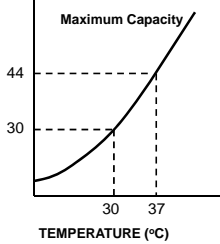


The body has to spend **Energy**:
 0.00003 cal to heat 1°C 1 ml CO₂
 577 cal to evaporize 1ml H₂O } **HYPOTHERMIA**

Desiccation and Cooling are intimately associated

Humidity and Temperature

ABSOLUTE HUMIDITY (mg/L)



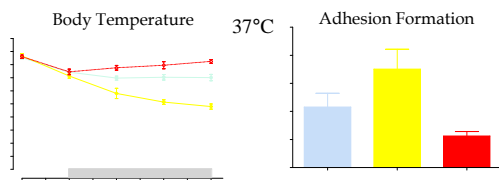
✓ Warming the gas increases its capacity to hold vapour

✓ Therefore, desiccation is higher at higher temperatures.

✓ Then it is not good to use warm and dry gas as several studies suggested.

CO₂ pneumoperitoneum is a cofactor in adhesion formation

5. Desiccation and cooling

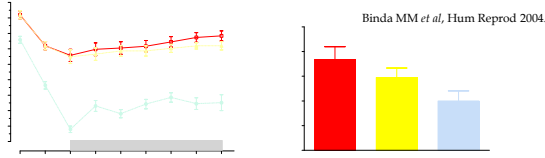


p<0.0001: 23 vs 493 ml/min flow and 493ml/min flow hum vs non-hum Two way ANOVA

* p=0.02 Mann Whitney

CO₂ pneumoperitoneum is a cofactor in adhesion formation

6. Hypothermia reduces adhesion



Two way ANOVA
^a p<0.01 vs group I
^b p<0.0001 vs group II

P=0.02, Pearson

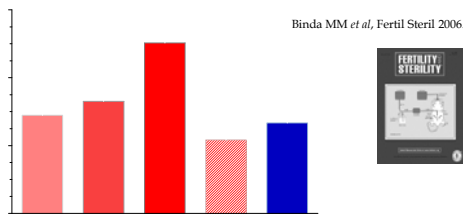
Experimental design: 60 min CO₂ PP, humidified gas for PP, little flow = No desiccation, Chamber at 37°C, modulate mouse body temperature: around 37°C; ventilation with humidified gas, around 36°C; ventilation with non-humidified gas, around 32°C; placing mouse in/outside the 37°C chamber

Why hypothermia reduces adhesions?

- > Hypothermia protects from the toxic effects of hypoxia and the ischemia/reperfusion process.
 - > Reduces metabolic activity (oxygen consumption)
 - > Decreases metabolic rate during ischemia
 - > Reduces reactive oxygen species (ROS) production during reperfusion
 - > Improves recovery of energetic parameters during reperfusion
- > Hypothermia reduces the inflammatory response:
 - ↓infiltration of PMN, ↓ TNF-α, ↓ IL-1.
- > Hypothermia increases intestinal peristalsis.

CO₂ pneumoperitoneum is a cofactor in adhesion formation

7. Desiccation without cooling increases AF



Binda MM *et al*, Fertil Steril 2006.

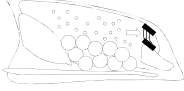


| | I | II | III | IV | V | |
|----------------|----------|----------|----------|----------|----------|--|
| Flow (ml/m) | 0 | 23 | 100 | 100 | 100 | |
| Hum. gas | No | No | No | Yes | No | |
| Hypothermia | No | No | No | No | Yes | |
| Temp during PP | 37.9±0.2 | 37.7±0.2 | 38.1±0.2 | 38.9±0.2 | 32.7±0.3 | |
| PPT - BT | 0 | 0 | 0 | 0.6±0.1 | 0 | |
| PPRH (%) | 100 | 100 | 100 | 100 | 100 | |

Wilcoxon
^a p<0.05 vs group I
^b p<0.05 vs group III

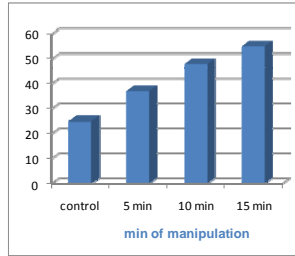
Peritoneal cavity as a cofactor in adhesion formation

8. Manipulation during surgery increases AF



► Manipulation at the bowel and omentum during pneumoperitoneum increases AF at the lesion site.

(Schonman R *et al*, JMIG 2009)



Peritoneal cavity as a cofactor in adhesion formation

9. Acute inflammation and AF are correlated

TABLE 1

Correlation between adhesion and inflammation scores.

| Inflammatory parameters | Biopsy location | Adhesion score (P value) | | | | Proportion (%) |
|-------------------------|-----------------|--------------------------|--------|--------|----------|----------------|
| | | Total | Extent | Type | Tenacity | |
| Neovascularization | Central | .0002 | NS | <.0001 | .0032 | NS |
| | Surrounding | .0002 | NS | <.0001 | .0021 | NS |
| Permeability | Central | .0091 | NS | .0111 | NS | NS |
| | Surrounding | .0286 | NS | .0382 | NS | NS |
| Leukocytes accumulation | Central | .0003 | .0043 | .0029 | <.0001 | .0031 |
| | Surrounding | .0002 | .0032 | .0021 | <.0001 | .0028 |
| Total score | Central | <.0001* | .0017 | <.0001 | <.0001 | .0005 |
| | Surrounding | <.0001* | .0005 | <.0001 | <.0001 | .0005 |

Note: Spearman correlation was performed. NS = not statistically significant.

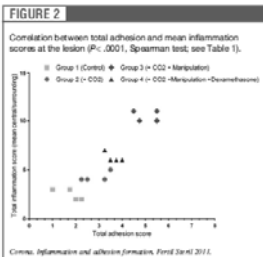
* Data shown in Figure 2.

Corona. Inflammation and adhesion formation. Fertil Steril 2011.

(Corona R *et al*, Fertility & Sterility 2011)

Peritoneal cavity as a cofactor in adhesion formation

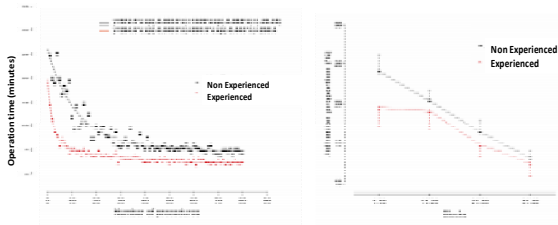
9. Acute inflammation and AF are correlated



(Corona R *et al*, Fertility & Sterility 2011)

Surgeon Skills & Adhesions

10. Learning curve decreases AF



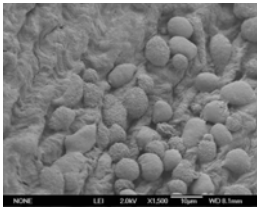
(Corona R et al, Fertility & Sterility in press 2011)

Importance of surgeon training

Peritoneal cavity as a cofactor in adhesion formation

“Conditioning of the abdominal cavity”

- ✓ Humidified gas = No desiccation
- ✓ Adding 3% oxygen to the PP = Avoid hypoxia
- ✓ Low body temperature locally = Avoid hypoxia; reduces inflammation

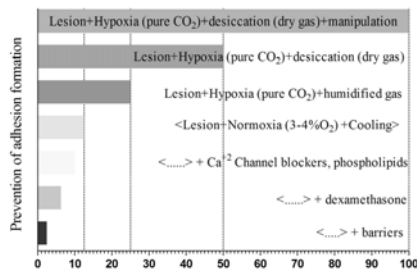


Less mesothelial cell damage, less adhesions

Mesothelial layer SEM after using non-humidified gas (Risikjaer, Binda, Koninckx unpublished observations)

Peritoneal cavity as a cofactor in adhesion formation

“Conditioning of the abdominal cavity + products”



Conclusions: *New concepts in adhesion prevention:*

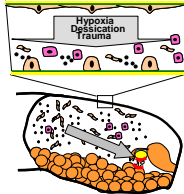
1) Peritoneal cavity as a cofactor

Repair of a surgical lesions is strongly influenced

By factors coming from the entire peritoneal cavity

Bad factors= acute inflammation

- Increased by:
 - hypoxia, hyperoxia
 - Desiccation
 - Mechanical trauma, blood



- Decreased by:
 - Lower temperature
 - Dexamethasone
 - New insufflation gaz mixtures

Conclusions: *New concepts in adhesion prevention:*

2) A less traumatic pneumoperitoneum (humidified gas, low temperature locally and different gases) combined with adhesion prevention products (dexamethasone, barriers) should be used to get up to 90% adhesion reduction

Thanks for your attention

ADHESIONS AND REPRODUCTION.

S. GORDTS

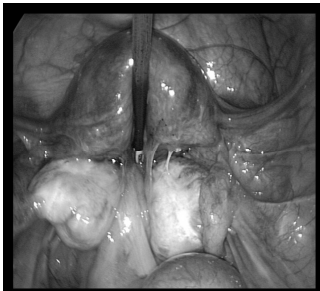
ESHRE Stockholm 2011.



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Conflict of interest: cons. Storz

ADHESIONS AND REPRODUCTION.



Disease

- Infection
- Endometriosis

Iatrogenic

- Surgery: de novo reformation



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Postoperative Adhesions

Surgical trauma operative site + other organs

Manipulation, foreign material, talk, drying, sponging



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Most frequent involved organ

OVARY

SINGLE MESOTHELIAL LAYER



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SCAR study (Surgical and Clinical Adhesions Research)

Laparotomy: 93% adhesion formation
(Mensies&Elles, 1990)

85 % reformation of adhesions
(Diamond & Freedman 2001)

15 – 20 % of cases of secondary infertility
(Liakakos 2001)



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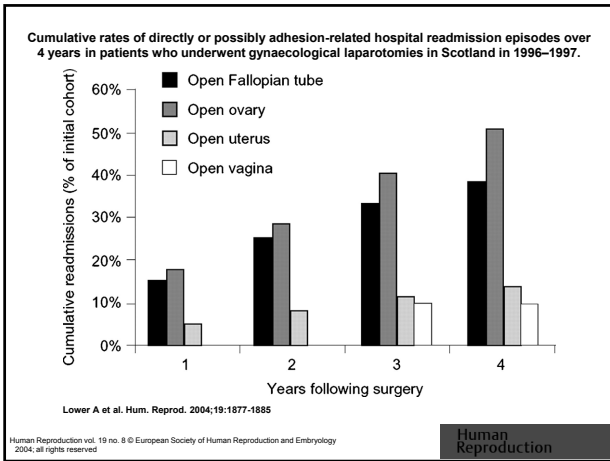
ADHESIONS AND REPRODUCTION.

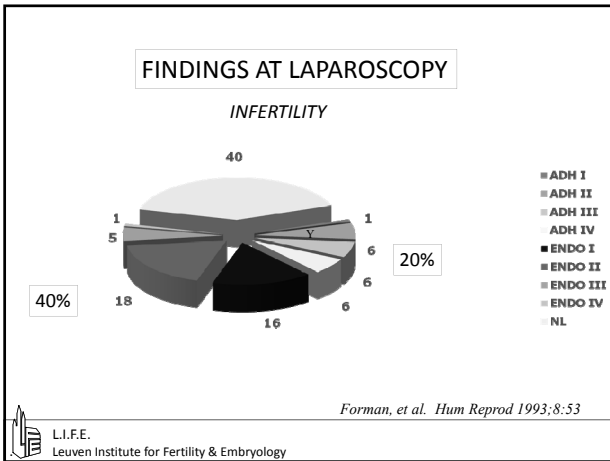
| | |
|---------|---------------------|
| Causing | Infertility |
| | Chronic pelvic pain |
| | Bowel obstruction |
| | Re-operation |

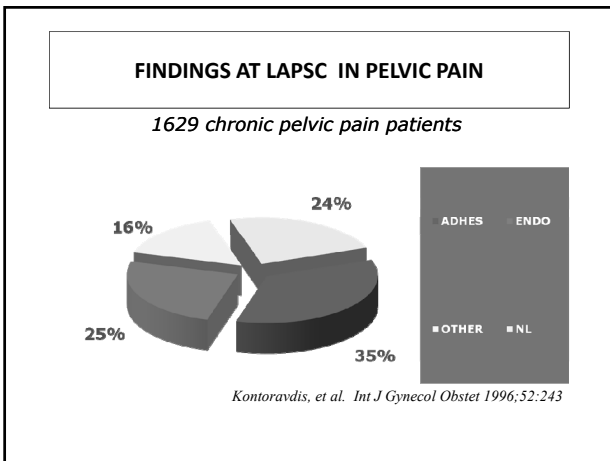


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Laparotomy

Conventional macrosurgical technique

associated with

inflammation, trauma and
foreign materials (sutures) leading to

- tissue ischemia and adhesion formation
- failure of the intrinsic peritoneal fibrinolysis

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Microsurgical Techniques

gentle tissue handling

Kurt Semm
Victor Gomel
Robert Winston
Ivo Brosens

TUBAL REANASTOMOSIS

Figure 6.3 The surgeon and the assistant sit comfortably with their legs under the table extension and not against the central pedestal.

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Microsurgery and Gentle tissue handling

Material and methods

Magnification: Operative microscope

Microsurgical Instruments

Suture material: 7/0 - 8/0

Training: well mastered surgical technique

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Microsurgery and Gentle tissue handling

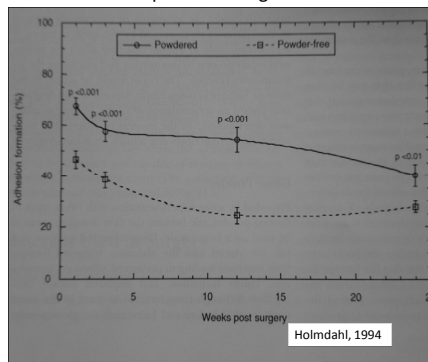
Material and methods

- Continuous irrigation to avoid tissue from drying
- Complete resection of pathological tissue
- Atraumatic manipulation of tubal serosa and mucosa
- Complete restoration of the serosa, avoid traction
- Avoid bleeding
- Selective bipolar coagulation



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Adhesion formation: experimental rat model Powder versus powder free gloves



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Adhesion formation: experimental rat model Powder versus powder free latex and synthetic gloves

Dwivedi *et al.* 2004 *Am J Surg*

| | |
|------------------------|------------------|
| Synthetic powder free: | adhesions 0 |
| Synthetic powdered: | adhesions ++ |
| Latex powdered free: | adhesions +++ |
| Latex powdered: | adhesions ++++++ |

$p < 0.05$

Correlated with cytokine expression



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LAPAROSCOPY !!!!!

Minimal access

No open abdomen

Laparoscopy versus laparotomy

Human

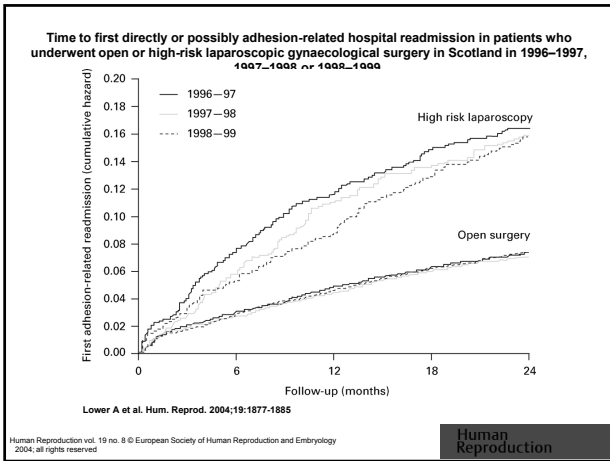
| | | | |
|-------------------------------|------|-------|----------------|
| Lundorff <i>et al.</i> , 1991 | 58% | 79% | ectopic |
| Audebert <i>et al.</i> , 2000 | 1,6% | 51,7% | abdominal wall |
| Levrant <i>et al.</i> , 2000 | 0% | 59% | abdominal wall |

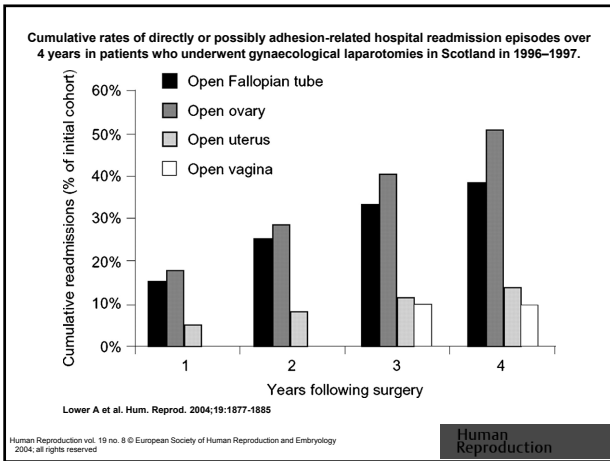
Laparoscopy versus laparotomy

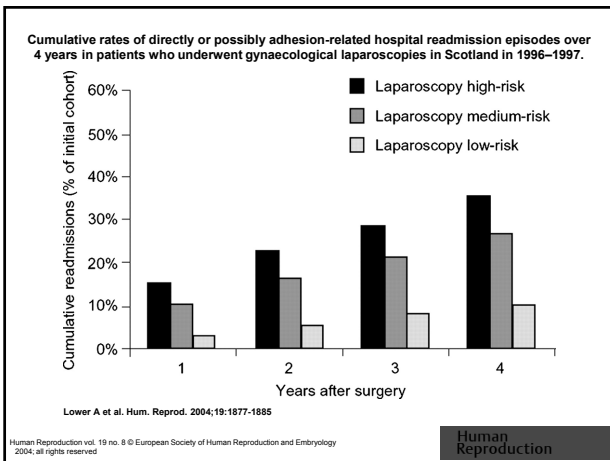
Animal

No difference: Marana *et al.*, 1994
Jorgensen *et al.*, 1995
Jacobi *et al.*, 2001
Filmar *et al.*, 1987

Favouring laparoscopy: Luciano *et al.*, 1989
Moore *et al.*, 1995
Chen *et al.*, 1998
Garrard *et al.*, 1999
Tittel *et al.*, 2001







Readmission after laparotomy / laparoscopy

| Re-admission | open | lapsc |
|--------------|------|-------|
| High risk | 1/6 | 1/7 |
| Medium | 1/7 | 1/10 |
| Low | 1/20 | 1/40 |

Lower A et al. Hum. Reprod. 2004;19:1877-1885

Microsurgery



Minimal access

Effort for LESS tissue DAMAGE

Necessity of application of gentle tissue handling at laparoscopy

- Bipolar
- Carbon dioxide (CO2) laser + precision
- Meticulous technique that maintains serosal integrity may reduce the incidence of de novo adhesions formation

TABLE 1
CLASSIFICATION OF ADHESIAL ADHESIONS

| Adhesions | Frequency | Distortion |
|-----------|-----------|------------|
| 1 | 2 | 0 |
| 2 | 4 | 0 |
| 3 | 2 | 0 |
| 4 | 1 | 0 |

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Fertil Steril 1988; 49

TRANSVAGINAL ENDOSCOPY

DIAGNOSTIC ACCURACY

Subtle (endometriotic) ovarian adhesions

| | mild endometriosis | Unexplained Infertility |
|--------------------|--------------------|-------------------------|
| S. laparoscopy | 40% | 0% |
| Transv.laparoscopy | 70% | 45 % |

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ADHESIONS AND REPRODUCTION.

Interference

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Endometriosis as a Pleiotropic Reproductive Disorder

- Endometriotic lesions
- Peritoneal inflammatory microenvironment
- Subtle ovarian dysfunctions
- Aberrant endometrial SSH response
- Myometrial JZ hyperplasia and dysfunction

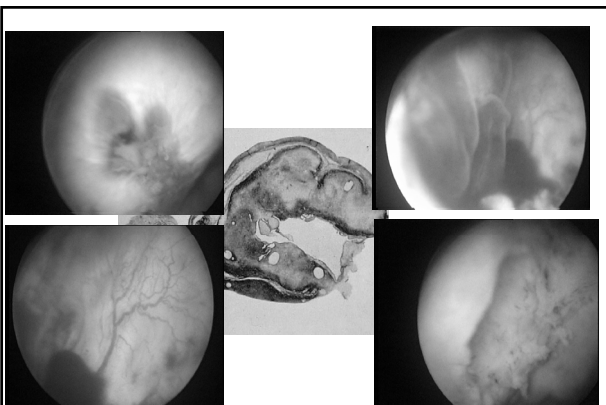
Endometriosis Probability of spontaneous conception?

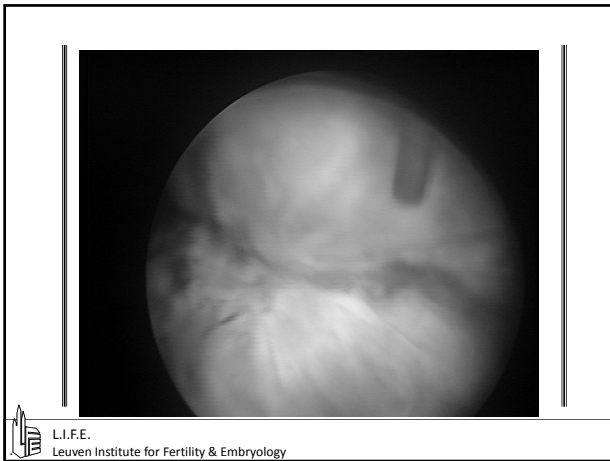
Minimal endometriosis

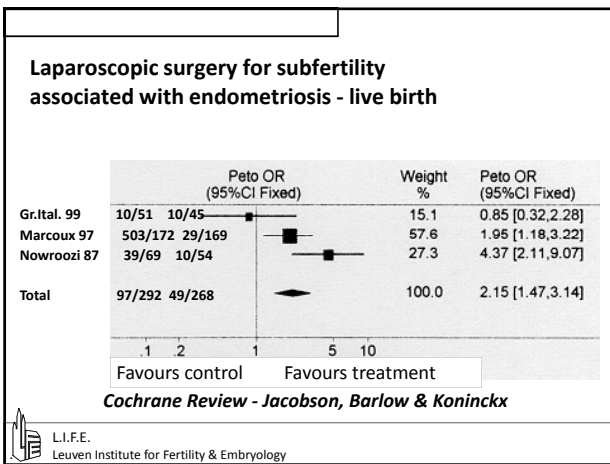
| | |
|------------------|--------|
| Marcoux et al. | 18 % |
| Parazzini et al. | 22 % |
| Adamson et al. | 37.4 % |

Moderate and severe (III-IV)

| | |
|-----------------|-------|
| Adamson et al. | 3.1 % |
| P. Barri et al. | 11% |







ENDOMETRIOSIS-Associated INFERTILITY

Comparison of Pregnancy Rates (Adamson, Sem Reprod Endocrin 1997)

| | Stage of disease | |
|-------------|------------------|--------|
| | Mini/Mild | Severe |
| • Expectant | 37,4% | 3,1% |
| • Surgical | 51,7% | 41,3% |

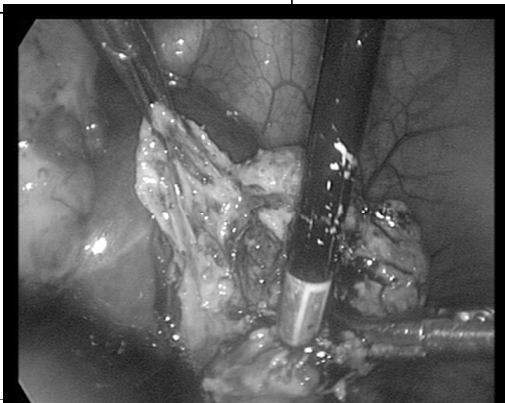
L.I.F.E.
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Endometriosis
Conservative surgery

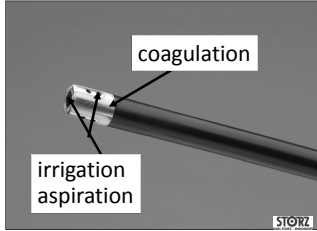
- Elimination of implants and adhesions
- Effective in infertility and CPP, but more in severe than mild disease

TECHNIQUES FOR RECONSTRUCTIVE
OVARIAN SURGERY IN ENDOMETRIOSIS

1. EVERSION
2. EXCISION



BIPOLAR COAGULATION PROBE



Three in one

- Easy handling
- Good haemostasis
- Helpful dissection
- No carbonisation
- Minimal cost

RECONSTRUCTIVE OVARIAN SURGERY IN ENDOMETRIOSIS

| | Ablation | Excision |
|---------------|------------------|------------|
| | recurrence rates | |
| Hemmings 1998 | 8% (36) | 12% (23) |
| Saleh 1999 | 21.9% (70) | 6.1% (161) |
| Beretta 1998 | 18.8% (32) | 6.2% (32) |
| Fayez 1991 | 33% (30) | 29% (66) |

TECHNIQUES FOR RECONSTRUCTIVE OVARIAN SURGERY IN ENDOMETRIOSIS

1. EVERSION

Three steps:

1. Adhesiolysis
2. Wide opening at site of inversion
3. Superficial coagulation endometriotic implants

TECHNIQUES FOR RECONSTRUCTIVE
OVARIAN SURGERY IN ENDOMETRIOSIS

2. EXCISION

Three steps:

1. Adhesiolysis
2. Wide opening at site of inversion
3. Resection of fibrotic pseudo-capsule

Eversion/ablation \neq fenestration

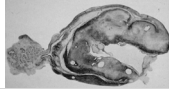
Opening is at site of inversion with resection of
fibrotic edges

Eversion or Excision technique:

Cysts > 5 cm: 2 step operative procedure

TECHNIQUES FOR RECONSTRUCTIVE OVARIAN SURGERY IN ENDOMETRIOSIS

Everson versus Excision



Excision: higher incidence adhesion formation
lower recurrence rate
Reduced ovarian volume and ovarian reserve

(El-Shawi, 1998; Al-Azemi, 2000; Nargund 1995; Loh, 1999)

Everson: higher recurrence rates ?



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Decline of AMH after cystectomy for ovarian endometrioma

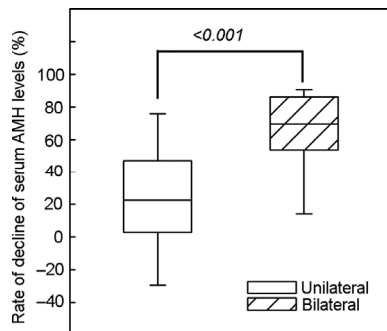
| Characteristics | Overall (n=38) | Unilateral (n=20) | Bilateral (n=18) | P-value |
|--------------------------|----------------|-------------------|------------------|---------|
| Age | 33.8 ±4.7 | 34.0 ±3.9 | 33.6 ±5.4 | 0.830 |
| BMI (kg/m ²) | 20.1±2.3 | 20.4±2.7 | 19.7±1.7 | 0.781 |
| Serum AMH | | | | |
| Pre-operative | 3.9±2.5 | 4.1±2.3 | 3.6±2.7 | 0.299 |
| Post-operative | 2.1±1.6 | 2.9±1.6 | 1.2±1.0 | 0.001 |

Hirokawa et al. Hum Reprod 2011; 26, 4



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The rate of decline in serum AMH is defined as $100 \times \frac{[\text{preoperative AMH level} - \text{post-operative AMH level}]}{\text{preoperative AMH level}}$.



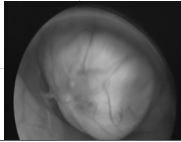
Hirokawa W et al. Hum. Reprod. 2011;26:904-910

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Human
Reproduction

Tubal surgery

- Distal occlusion
- Proximal occlusion
infectious / mechanical
- Ectopic



Salpingostomy

Microsurgery

| | Year | Nb | IUP % | E.P % |
|-------------|------|-----|-------|-------|
| Leuven | 1980 | 333 | 21 | 6 |
| Winston | 1980 | 241 | 24.5 | 9.5 |
| Verhoeven | 1983 | 143 | 23.7 | 2 |
| Boer Meisel | 1986 | 108 | 28.7 | 17.5 |
| Gomel | 1978 | 89 | 31 | 9 |
| Dubuisson | 1985 | 76 | 36 | 22 |

Salpingostomy

Laparoscopy

| | Year | Nb | IUP % | E.P % |
|-----------|------|-----|-------|-------|
| Dubuisson | 1990 | 65 | 27.7 | 4 |
| Donnez | 1994 | 85 | 27 | |
| Filippini | 1996 | 104 | 32.5 | 4.8 |
| Canis | 1991 | 87 | 33.3 | 6.9 |
| Audebert | 1992 | 142 | 20.4 | |

Salpingostomy

Laparoscopy >< microsurgery

Pregnancy rates

| grade | I | II | III | IV |
|--------------|------|------|------|-----|
| laparoscopy | 50 | 32.4 | 8.3 | 0 |
| microsurgery | 66.6 | 36.6 | 14.3 | 7.7 |

1991 Canis et al.

Salpingoscopy

| Grade | Intrauterine pregnancy rate | Ecopic pregnancy rate |
|-------|-----------------------------|-----------------------|
| I | 53% | 5% |
| II | 20% | 10% |
| III | <5% | 50% |
| IV | | |

Brosens, Reprod. med. Rev. 1996, 5:1

ADHESIOLYSIS

LAPAROSCOPY

| | N | % IUP |
|--------|-----|-------|
| Bruhat | 93 | 51 |
| Gomel | 92 | 62 |
| Donnez | 186 | 58 |
| Fayez | 50 | 60 |

Tubal surgery

- Distal occlusion
- Proximal occlusion
infectious / mechanical
- Ectopic

Tubal microsurgical anastomosis

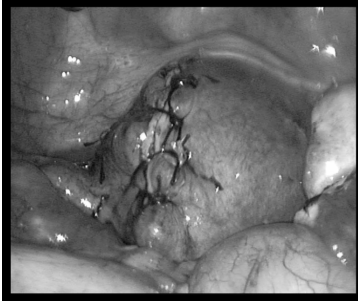
Reversals

| | Year | Nb | IUP % | E.P % |
|-----------|------|-----|-------|-------|
| Winston | 1980 | 126 | 60.4 | 2.4 |
| Gomel | 1980 | 118 | 82.5 | 1.7 |
| Rock | 1982 | 125 | 65.0 | 4.0 |
| Schlösser | 1983 | 119 | 60.5 | 2.5 |
| Dubuisson | 1995 | 206 | 69.9 | - |
| Boeckx | 1986 | 63 | 69.8 | 5 |

Tubo cornual anastomosis

| | Year | Nb | IUP % | E.P % |
|---------|------|----|-------|-------|
| Diamond | 1979 | 28 | 75 | 0 |
| Mc Comb | 1980 | 38 | 55 | 5 |
| Winston | 1980 | 43 | 60 | 2.5 |
| Fayez | 1982 | 20 | 55 | 5 |

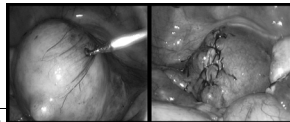
Myomectomy



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Myomectomy and adhesion formation

| | | | |
|---|-------|--------------------|-------|
| Tulandi 1993 | | | |
| <i>Obst Gynaec</i> 82; 213 | n= 26 | posterior incision | 93.7% |
| | | anterior/fundal | 55.5% |
| Ugur 1996 | | | |
| <i>Int J Obst Gynaec</i> 53; 145 | n= 48 | laparotomy | 83.3% |
| adhesions +++ posterior/size/intra-mural/nb | | | |



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Myomectomy and adhesion formation

Laparoscopy

| | | |
|-------------------------|--------|-------|
| Stringer et al. (1997) | n= 50 | 58% |
| Nezhat et al.(1991) | n= 154 | 54% |
| Hasson et al. (1992) | n= 56 | 67% |
| Dubuisson et al. (1994) | n= 102 | 11.8% |
| Keckstein et al. (1994) | n= 22 | 28% |
| Takeuchi et al.(2002) | n=51 | 29.4% |

Mean incidence: 45 – 50%

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Myomectomy and adhesion formation

Adhesion favouring factors

Operative technique and skill
Suture material
Posterior uterine incision
Intramural myoma
Numbers incision

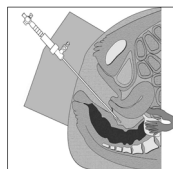
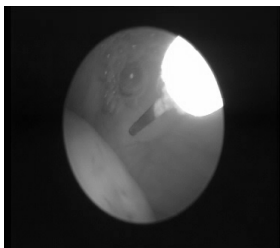
Surgical treatment of patients with PCO related infertility

Wedge resection (Stein-Leventhal, 1935)
Laparoscopic procedures
 biopsy
 electrocautery
 laser
Transvaginal laparoscopic procedures
 bipolar current

Mean pregn. rate: 63%

Surgical treatment of patients with PCO related infertility

Transvaginal laparoscopic ovarian capsule drilling



Easy; low morbidity
Minimal trauma
Watery environment

Surgical treatment of patients with PCO related infertility

Adhesion formation

| | | | |
|------------------------|-------|---------------|-----|
| Naether, Fisher (1993) | n=62 | cauterization | 19% |
| Naether et al. (1994) | n=26 | cauterization | 27% |
| Liquori et al.(1996) | n=30 | cauterization | 23% |
| Felemban et al.(2000) | n=15 | cauterization | 26% |
| Saravelos et al.(1996) | n=21 | cauterization | 33% |
| Weise et al. (1991) | n= 10 | cauterization | 70% |
| Gürkan et al. (1992) | n=20 | Nd:Yag | 68% |
| Grochmal (1988) | n=30 | Nd:Yag | 3% |
| Keckstein (1990) | n=11 | Nd:Yag | 0% |
| | n=19 | CO2 laser | 15% |



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Risks adhesion formation



Leuven Institute for Fertility and Embryology

Conclusion

- Adhesions have are very frequent in the female pelvis
- Large impact on reproductive performance
- No clear evidence of less adhesion formation after laparoscopy



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Conclusion

PREVENTION:

- Correct indication
- Correct technically performed surgery
- Microsurgical principles: minimal tissue damage
 - minimal bleeding
 - minimal coagulation
 - gentle tissue handling
 - avoiding desiccation
 - keep organs wet
 - time management
- Use of barriers



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Reproductive surgery:

Difficult and challenging

Good surgery is the best prevention
Necessity for training



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Stephan Gordts
Rudi Campo
Patrick Puttemans
Sylvie Gordts
Marion Valkenburg
Caroline Van Turnhout



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Adhesions prophylaxis in routine clinical practice: lessons learned from experimental models to clinical applications

Luciano G. Nardo MD MRCOG

Director, Consultant Gynaecologist and Subspecialist in Reproductive Medicine & Surgery Manchester, UK



Conflict of interest

Shareholder/director: GyneHealth Ltd.

Shareholder/director: North West Fertility Ltd.

Shareholder/founder: Concepta



Abdominal adhesion prevention: still a sticky subject?

Lauder et al. *Dig Surg* 2010; 27:347

Adhesion formation following surgery remains an almost inevitable consequence of most abdominal procedures

Estimates on the workload for the treatment of adhesion-related disorders have put the annual cost in the USA at around \$1.3 billion

Healthcare costs

Medico-legal costs



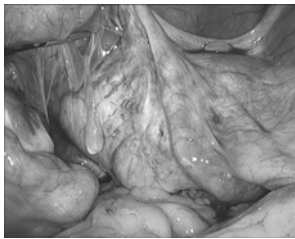
- **Congenital adhesions**

- **Acquired adhesions** (inflammatory process, radiation and/or surgery)

- **Primary adhesions**

- **Secondary adhesions**

Gyne)Health



Adhesions should be considered as highly cellular, vascularised and dynamic structures under the influence of complex signalling pathways

Gyne)Health

Adhesions prophylaxis

- 1) Reducing local effects at the level of surgical trauma

- 2) Minimising the adhesions effects of pneumoperitoneum

Gyne)Health

~ 90% of acquired adhesions are post-surgical

- Tissue trauma
- Electrosurgery (heating and dessication)
- Fluids
- Infection
- Ischaemia
- Foreign body reaction
- Bleeding

Menzies and Ellis, 1990
Menzies, 1992

Gyne)Health

Adhesions-related repeated surgeries are a common consequence of gynae procedures, and adhesiolysis is followed by a high incidence of adhesions reformation and de-novo adhesion formation

Diamond and Freeman, 2001

Gyne)Health

- **Bowel obstruction**
- **Infertility**
- **Pelvic pain**
- **Difficult re-surgery**
- **De-novo adhesions**

Gyne)Health

SCAR Study

29,790 patients

Open abdominal or pelvic surgery in Scotland

10-year period, and review of re-admissions

1/3 of patients were re-admitted a mean of 2.1 times

Open surgical procedures on the colon and rectum as well as on adnexal pathologies had the highest risk for adhesion-related re-admissions

Lower et al., 2004



INJURY TO THE PERITONEUM

Disruption of stromal mast cells, and release of histamine, vasoactive amines and cytokines (IL-1, IL-6 and TNF- α)

Attraction and activation of macrophages to secrete vasodilating substances

Transformation of inactive prothrombin into thrombin and conversion of fibrinogen into monomers of fibrin

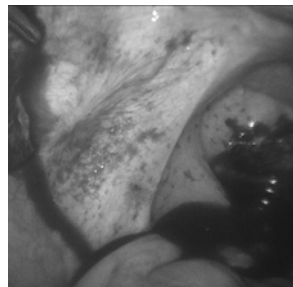
Platelets contribute to the fibrin clot and initiation of the coagulation cascade process

Increase in capillary permeability, formation of fibrous exudate



Blood and postoperative bleeding increases the fibrin deposition, most of which will disperse by fibrinolysis

The remaining fibrinous mass will result in the formation of adhesions



Peritoneal defects heal by a process of metaplasia from the underlying mesenchyme - migration of epithelial cells from the free peritoneal fluid and proliferation of epithelial cells from the defects margins

Macrophages contribute to the recruitment of mesothelial cells onto the injured surface, which in turn proliferate and cover the injured area

Gyne)Health

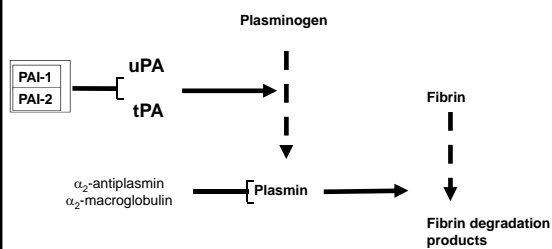
Substances released by the mesothelial cells and contributing to peritoneal healing and adhesion formation:

- Plasminogen activator
- Plasminogen activator inhibitor
- Arachidonic acid metabolites
- ROS
- Cytokines
- Collagenase
- VEGF

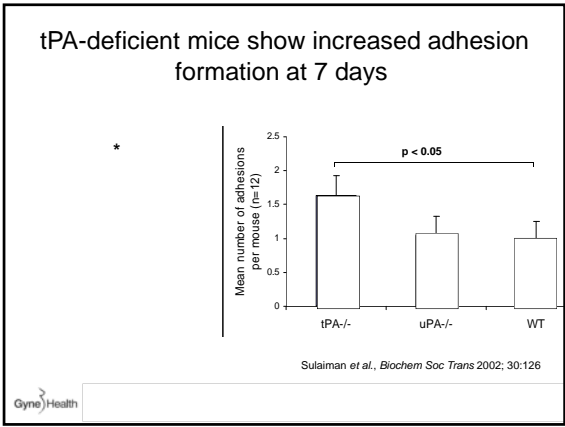
Rodgers and di Zerega, 1993
Binda et al., 2003
de Souza et al., 2003
Sutton et al., 2005

Gyne)Health

Fibrinolytic process begins 3 days after peritoneal injury and increases to a maximum by day 8



Gyne)Health




“Critical window”

Day 3 Day 8

Gyne)Health

Models of adhesion formation



- Animal model
- Lack of uniformity
- Methods to promote adhesion formation
- Severity scoring criteria
- Simplicity
- Reproducibility

Gyne)Health

Issues with Clinical Studies

Large cohort
*15000 subjects

Long follow-up
*42 weeks

***25% efficacy**

Wilson MS, Colorectal Dis 2007; 9:60

Gyne)Health

Table 1 Surgical techniques for prevention of adhesion formation.

- Minimizing surgical trauma
- Minimizing tissue handling
- Avoiding peritoneum suturing or use of fine non-reactive suture
- Achieving excellent haemostasis and avoiding local ischaemia
- Reducing drying or overheating of tissues
- Avoiding foreign bodies (talc, starch)
- Removing intra-peritoneal blood deposits
- Reducing infection risk



Pados et al., 2010

Gyne)Health

Keyhole versus open access

? Laparoscopy less adhesiogenic than laparotomy

Filmar et al., Fertil Steril 1987
Marana et al., AJOG 1994
Jorgensen et al., Aust NZJ Surg 1995

Peritoneal factors and trauma mechanisms enhance adhesions formation

Gyne)Health

- Oxygenation
- Anaerobic cell metabolism
- Acidosis
- ROS

Gyne)Health

Mouse model of surgical approach induced adhesion formation

Hypoxic (laparoscopy) model – pure CO₂
 Normoxia model – 3% oxygen added (pO₂ 23 mmHg)
 Hyperoxia (open surgery) model – 12% oxygen added

Molinas et al., Fertil Steril 2001
 Elkelani et al., Fertil Steril 2004

Dose and length dependent

Gyne)Health

Anti-adhesive agents:

- Pharmacological
 - systemic
 - intra-peritoneal
- Intraperitoneal barriers
 - solid
 - liquid

Safe
Effective
Economical
Easy to use
Readily available

Gyne)Health

Table 2 Pharmacological anti-adhesive agents.

| Type | Examples |
|--------------------------|---|
| Fibrinolytic agents | Fibrinolysin Papain Streptokinase, streptodase Urokinase Hyaluronidase: Chymotrypsin, trypsin, pepsin Elastase |
| Anticoagulants | Recombinant tissue plasminogen activator Heparin Citrate |
| Anti-inflammatory agents | Corticosteroids Antihistamines Non-steroidal anti-inflammatory drugs |
| Antibiotics | Tetracycline Cephalexin |
| Other agents | Progesterone Oestrogens Gonadotrophin-releasing hormone agonists Antiproliferative agents Aromatase inhibitors Statins Metastatin |

Pados et al., 2010

Gyne)Health

- Limitation of fibrin deposition
- Amplification of fibrin absorption
- Suppression of fibroblast activity
- Maintenance of adequate blood supply

Prevention of postoperative peritoneal adhesions by administration of estrogen
Bozkurt et al. *J Invest Surg* 2009; 22:263

60 Wistar albino rats

- Control group
- Saline group
- Estrogen group

Adhesion formation and peritoneal leucocyte count were significantly less in the estrogen group as compared with the other two groups

Gyne)Health

A novel polypeptide derived from human lactoferrin in sodium hyaluronate prevents postsurgical adhesion formation in the rat
Nilsson et al. *Ann Surg* 2009; 250:1021

PXL01 (a peptide derived from human lactoferrin)
Anti-inflammatory and fibrinolytic activities
Large bowel anastomosis

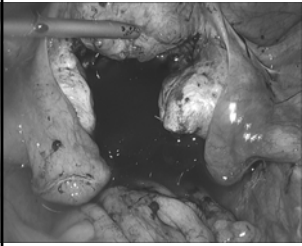
Reducing infection, prohibiting inflammation and promoting fibrinolysis

Reducing formation of peritoneal adhesions

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Table 3 Anti-adhesion barrier methods

| Type | Examples |
|---------------------------------|--|
| Fluid barriers | Various oils Liquid paraffin Amniotic fluid Crystalloid solutions Dextran Icodextrin 4% Polyglycan esters |
| Solid barriers (membranes, gel) | Omental grafts Peritoneal grafts Bladder strips Fetal membranes |
| Endogenous tissue | Silicone Vasectine Gelatin Metal foils Flax® and silk foils Expāderc polytetrafluoroethylene Oxidized regenerated cellulose Hyaluronic acid Carboxymethylcellulose Polyethylene glycol Polylactide Fibrin, N,O-carboxymethylchitosan |
| Exogenous material | |



Pados et al., 2010

GyneHealth

A hydrogel for adhesion prevention: characterization and efficacy study in a rabbit uterus model
 Muller et al. *Eur J Obstet Gynecol Reprod Biol* 2010 [Epub ahead of print]

A physically cross-linked polyvinyl alcohol and carboxymethylcellulose (PVA/CMC) hydrogel
 Icodextrin 4% solution
 Untreated control group

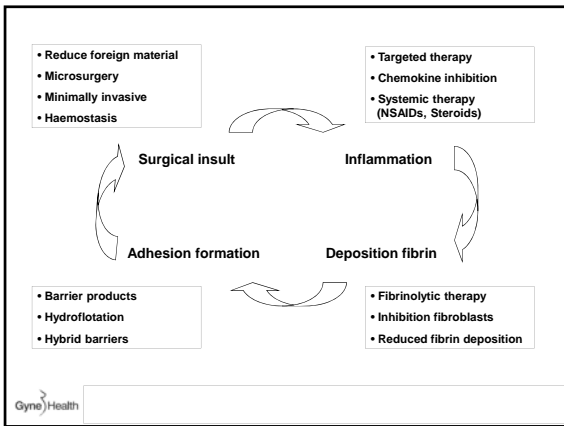
In vivo experiments showed a reduction in incidence, extent and severity of adhesions after use of hydrogel as compared to the other groups

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Ideal anti-adhesive pharmacological agents and barriers

- Reduce adhesion formation over current treatments
- Target key events in adhesion formation (close approximation of damaged surfaces and/or reduced fibrinolysis)
- Allow normal healing at distant sites (bowel anastomosis, laparotomy scar, endometriosis excision, adhesiolysis, etc.)
- Effect lasts for at least 48 hours after initiation of adhesion formation and possibly up to 7 days

GyneHealth



Available online at www.elsevier.com/locate/jbiomech
ScienceDirect
Biomaterials 25 (2004) 1564–1573
www.elsevier.com/locate/jbiomech

Peritoneal adhesion prevention with an *in situ* cross-linkable hyaluronic gel containing tissue-type plasminogen activator in a rabbit repeated-injury model
Yoon Yoo*, Inyoung Bae^a, Chulwon B. Bhattar^a, Robert Langer^b, Daniel S. Kohane^{a,b}

^aDepartment of Chemical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, US
^bDepartment for Biomedical and Drug Delivery, University of Manchester, Oxford Road, Manchester, M13 9PL, UK

The efficacy of a hyaluronate-carboxymethylcellulose bioresorbable membrane that reduces postoperative adhesions is increased by the intra-operative co-administration of a neurokinin 1 receptor antagonist in a rat model
Rafiq Ullah, MSc, Arthur F. Hristova, PhD, Jonathan W. Woodell, MS, Karen L. Reed, PhD, Ross Lynch, BS, and James W. Beatty, MS, PhD, Boston, MA

Available online at www.elsevier.com/locate/jbiomech
ScienceDirect
European Journal of Pharmacology and Biopharmaceutics 51 (2006) 17–26
www.elsevier.com/locate/jbiomech

Review article
Polymers in the prevention of peritoneal adhesions
Yoon Yoo*, Daniel S. Kohane^{a,b}

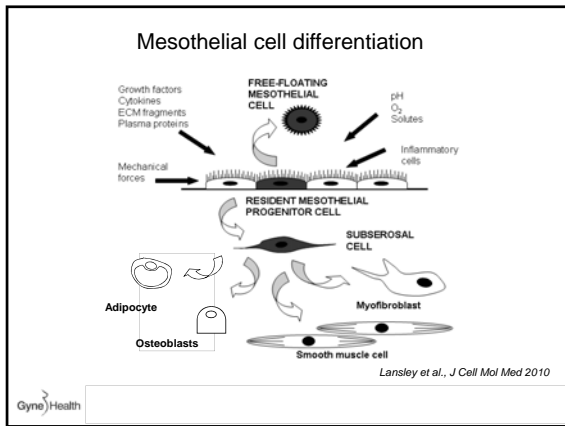
^a School of Chemical and Pharmaceutical Sciences, Faculty School of Biomedical Engineering, Purdue University, West Lafayette, IN, USA
^b Laboratory for Biomedical and Drug Delivery, Department of Biotechnology, University of Oxford, Oxford, UK
Daniel S. Kohane, Harvard Medical School Boston, MA, USA

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Incorporation of isolated free-floating mesothelial cells on denuded surface

Foley-Cramer et al., *J Cell Sci* 2002; 115:1383

GyneHealth





Postoperative intra-uterine adhesions: why?

Pietro Gambadauro, MD
Senior Consultant in Gynaecology and Reproductive Medicine
Centre for Reproduction
Uppsala University Hospital, Uppsala, Sweden



The author declares no conflict of interest

learning objectives

- to understand the mechanism of intrauterine adhesions
- to get awareness of procedures at higher risk for postoperative adhesions
- to be able to identify, counsel and properly follow-up patients at risk for intrauterine adhesions development

overview

- postoperative adhesions in gynaecology
- mechanisms of adhesion
- which surgery causes intrauterine adhesions?
- which patients develop adhesions?
- conclusions

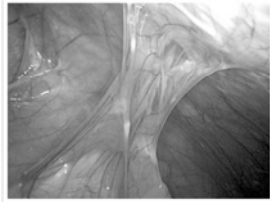
Postoperative adhesions in gynaecology

adhesions in gynaecology

- Scar tissue which develops at the site of tissue injury after surgery.
- Although commonly considered inevitable, they represent short/long term complications with important repercussions on patients' health and quality of life.
- Relevant direct and indirect costs.
- Adhesions in gynecology have a particular relevance
 - abdominal/pelvic pain
 - bowel obstruction
 - **infertility**

adhesions in gynaecology

- **70%-95%** of patients undergoing major gynecologic surgery. (Davey & Maher, 2007)
- Barrier agents for adhesion prevention after gynaecological surgery. (Ahmed G, et al. Cochrane Rev 2008)
- **Main focus on peritoneal adhesions.**
- Many surgeons operate in the abdomen but only us gynaecologists operate in the uterus.
- moreover, intrauterine adhesions might be less invalidating, but still extremely relevant in reproductive medicine.



<http://www.adhesions.com/01/01/Adhesions.jpg>
Image in the public domain

intrauterine adhesions

- **Systematic pre-IVF outpatient hysteroscopy** in patients with normal findings at HSG shows **4.1%** of adhesions, whereas ultrasound could not detect any. (El-Mazny A et al. 2011)
- **Hysteroscopy** identifies intrauterine adhesions in **11%** of patients with **repeated failure of IVF-ET**, none of them suspected at standard TV ultrasound (Oliveira et al. 2003)
- Moreover, IUA are more frequent in patients with previous IVF failure (**7.8%**) than in patients at the first attempt (**2.1%**) (El-Mazny A et al. 2011)

intrauterine adhesions

- IUAs are probably **underdiagnosed**/overlooked.
- Moreover, not just "adhesions", but also **scar tissue** with **thin unresponsive endometrium** plays a role in reproduction (Shufaro Y et al. J Assist Reprod Genet 2008)
- In the extreme, the whole cavity has been scarred and occluded but even with relatively **few scars**, the endometrium may **fail to respond to estrogens**. (Klein SM, Garcia CR. Fertility and Sterility 1973)

intrauterine adhesions

Better awareness together with an improved knowledge about etiopathogenesis would ideally lead to:

- Primary **prevention**: avoid interventions that cause adhesions or develop alternative strategies
- Secondary prevention/early **diagnosis**: early treatment, young adhesions are not as the old ones and adhesions might occur later than we believe. (Shokeir et al. 2008)
- Etiological **treatment**

The American Fertility Society classification of intrauterine adhesions, 1988.

| Extent of cavity involved | <1/3 | 1/3-2/3 | >2/3 |
|---------------------------|--------|-----------------|-------------|
| | 1 | 2 | 4 |
| Type of adhesions | Filmy | Filmy and dense | Dense |
| | 1 | 2 | 4 |
| Menstrual pattern | Normal | Hypomenorrhea | Amenorrhoea |
| | 0 | 2 | 4 |
| Prognostic classification | | | |
| Stage I (mild) | 1-4 | | |
| Stage II (moderate) | 5-8 | | |
| Stage III (severe) | 9-12 | | |

The American Fertility Society, 1988

Valle & Sciarra 1988

| | |
|----------|---|
| Mild | Filmy adhesion composed of basal endometrium producing partial or complete uterine cavity occlusion |
| Moderate | Fibromuscular adhesions that are characteristically thick, still covered by endometrium that may bleed on division, partially or totally occluding the uterine cavity |
| Severe | Composed of connective tissue with no endometrial lining and likely to bleed upon division, partially or totally occluding the uterine cavity |

Valle & Sciarra, 1988

European Society for Hysteroscopy classification of intrauterine adhesions (Wamsteker 1989)

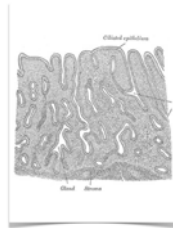
| | |
|------|---|
| I | Thin or filmy adhesion Easily ruptured by hysteroscope sheath alone Cornual areas normal |
| II | Singular firm adhesions Connecting separate parts of the uterine cavity Visualization of both tubal ostia possible Cannot be ruptured by hysteroscope sheath alone |
| IIa | Occluding adhesions only in the region of the internal cervical os Upper uterine cavity normal |
| III | Multiple firm adhesions Connecting separate parts of the uterine cavity Unilateral obliteration of ostial areas of the tubes |
| IIIa | Extension scarring of the uterine cavity wall with amenorrhoea or hypomenorrhoea |
| IIIb | Combination of III and IIIa |
| IV | Extensive firm adhesion with agglutination of uterine walls At least both tubal ostial areas occluded |

Eur Society for Hysteroscopy, 1989

Mechanism of adhesion

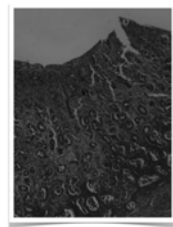
intrauterine adhesions

- The endometrium is composed of **two layers**, the **functional** layer which is shed during menstruation and an underlying **basal** layer which is necessary for regenerating the functional layer.
- The etiology of intrauterine adhesions (IUAs) is **multi-factorial**, as it recognizes multiple predisposing and causal factors (Baggish Barbot and Valle, 1999).
- **Trauma** to the basal layer can lead to the development of **intrauterine scars** resulting in **adhesions** which can obliterate the cavity to varying degrees.



surgical trauma

- Trauma to the basal layer is a key factor in the development of intrauterine scars resulting in adhesions.
- Amenorrhoea traumatica (atretica). Asherman JG. J Obstet Gynaecol Br Emp. 1948 Feb;55(1): 23-30.

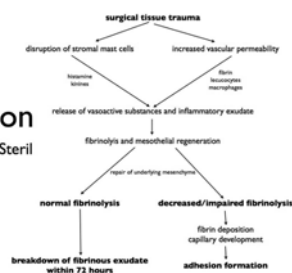


healing and adhesions

- Tissue healing process: Regeneration or Repair ?
- Post-surgical adhesions develop within the repair healing process in a similar way as scars. Scars are a consequence of a **repair mechanism that replaces the missing normal tissue** with an extracellular matrix (fibronectin and collagen types I and III). As such scarring represents a **failure of tissue regeneration**.
- **Fibrin** is deposited to seal the injury and initially builds **filmy**, "fibrinous" adhesions.
- **Fibrinolysis** may limit the extent of the initial fibrinous adhesion, and dissolve it.
- In case of **disruption** in the process of fibrinolysis, such a persistent or extended injury, **tissue repair cells** such as macrophages, fibroblasts and blood vessel cells, **penetrate into the fibrinous adhesion**, and lay down collagen and other matrix substances to form a **permanent fibrous adhesion**.

adhesion formation

ASRM Practice Committee. Fertil Steril 2007.

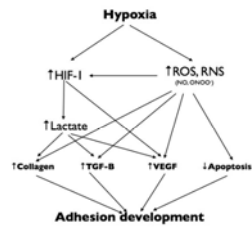


Hypoxia and Adhesiogenesis

- Although the mechanisms of adhesion development are incompletely understood, hypoxia appears to be a key causative factor, triggering a cascade of responses that leads to the creation of adhesions.
- Adhesions develop as a response to hypoxia whereby the body tries to reestablish oxygen and nutrient supply to tissues that have been injured by surgery or previous pathology. (Saeed & Diamond 2004)
- Therefore, adhesiogenesis is a culmination of increased extracellular matrix production associated with diminished matrix degradation, combined with decreased fibrinolytic activity. Thus surgical trauma, ischemia, or infection results in an increased incidence of adhesion through hypoxia, which dramatically diminishes fibrinolysis. (Saeed & Diamond Fertil Steril. 2003;79:164-168.)
- In vitro studies on a fibroblast culture system show how normal human peritoneal fibroblasts exposed to hypoxia manifest phenotypic changes characteristic of fibroblasts isolated from intraperitoneal adhesions.
- Acquisition of the adhesion phenotype by these fibroblasts appears to be irreversible. This might justify the clinical difficulty to prevent adhesion reformation. (Saeed & Diamond Fertil Steril 2002)

Hypoxia and adhesions

Valerie et al.
Review: Cellular Metabolism: Contribution to Postoperative Adhesion Development
Reproductive Sciences 2009;16:627



Which surgery causes intrauterine adhesions?

post-surgical intrauterine adhesions

- Virtually all kind of **intrauterine or transmural surgery** can cause intrauterine adhesions.
- **Intrauterine surgery:**
 - D&C
 - hysteroscopic surgery
- **abdominal uterine surgery:**
 - myomectomy with transmural incisions
 - cesarean section
 - uterine compression sutures/devascularization

post-pregnancy D&C

- The major cause of intrauterine adhesions.
- Risk of developing intrauterine adhesions following post-miscarriage D&C:
 - 9.3% (Cogendez 2011)
 - 19% (Friedler et al. 1993 Hum Reprod)
 - 37.6% (Salzani et al, 2007 Sao Paulo Med J)
- Surgical treatment of a missed abortion has a higher adhesiogenic potential when compared to incomplete miscarriage (31% vs 6.4%) (Schenker & Margalioth Fertil Steril 1982).
- Fibroblastic effect of retained products. (Deans & Abbott, 2010)

post-pregnancy D&C

- Incidence varies but can get as high as 40% after repeated D&C for placenta rests or incomplete miscarriage (Westendorp ICD et al., 1998)
- Approximately 90% of cases of IUA are related to post-partum or post-abortion *overzealous* D&C (Nappi et al. 2007)
- Use a suction catheter or blunt curette rather than a sharp instrument! (Yu et al. 2008)
- **But** IUAs are also possible following a *gentle* manual vacuum aspiration. (Dalton et al. Fertil Steril 2006)

post-pregnancy D&C

- Tam et al (2002) randomized 82 women with incomplete miscarriage to surgical or non-surgical management. Hysteroscopy at 6 months revealed respectively 7.7% and 0% adhesions.
- Ayas et al (2009) compared 60 patients with manual removal of the placenta, 60 patients submitted to post-partum curettage and 30 healthy controls. Hysteroscopically diagnosed adhesions were found respectively in 5%, 18.3% and 3.3% of the patients.
- The risk is considered lower following trauma to the non-pregnant uterus, with rates of intra-uterine adhesions estimated to be 1.6% after diagnostic curettage (Schenker & Margalioth 1982)

hysteroscopic surgery

- Considered a **minor factor** of adhesions when compared to d&c, but low awareness together with diagnostic pitfalls can justify an **underestimation** of the problem.
- Moreover, not all hysteroscopic surgery is the same:
 - resectoscope (thermal + mechanical injury)
 - monopolar
 - bipolar
 - operative hysteroscopy with microinstruments
 - diathermy
 - mechanical

hysteroscopic surgery

- Taskin et al (2000) showed a frequency of postsurgical intrauterine adhesions of **6.7%** after resection of uterine septa, **31.3%** after resection of a single myoma, and **45.5%** after resection of multiple myomas.
- Intrauterine adhesion is common following resection of **opposing submucous myomas**, but not for a solitary myoma (Yang et al. 2008 Fertil Steril)
- The incidence of uterine synechiae after **bipolar hysteroscopic resection** of fibroids was **7.5%**. This appears to be lower than that reported in previous studies using monopolar energy. Bipolar hysteroscopic myomectomy may be a better option for infertile women. (Touboul C et al. 2009)

hysteroscopic surgery

- Hysteroscopy for retained products of conception?
- Hysteroscopy **for directing curettage** (Goldenberg et al. 1997)
- **Hysteroscopic removal** of retained products of conception is a simple and safe, and most **probably the preferred procedure**. It should be considered an alternative to conventional blind evacuation by curettage. It seems that this procedure preserves the integrity of the uterine cavity while **averting additional trauma**, and retains reproductive capacity. (Golan et al. 2011)

hysteroscopic surgery

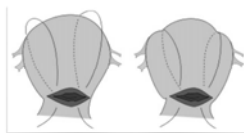
- An intentional form of intrauterine adhesions are those surgically induced by electrosurgical endometrial ablation. (Onoglu et al. 2007)
- IUAs also follow thermal (Leung et al. 2003) or microwave (Luo et al. 2010) endometrial ablation.
- But those adhesions cannot guarantee total loss of endometrial function neither protect against unintended pregnancies. (Hare & Olah, 2005)

abdominal surgery

- Abdominal surgery involving the uterus has also been implicated in the formation of intrauterine adhesions.
- **Transmural incisions**, such as during cesarean sections or myomectomies, can lead to the development of intrauterine adhesions (Nakhuda et al., 2005 J Gynecol Surg)
- The **risk** of intrauterine adhesions after cesarean delivery is estimated to be **2%**, and after laparotomy and full-thickness myomectomy is **1.3%**. (Schenker & Margalioth 1982)

uterine ischemia

- Asherman syndrome with complete obliteration of the uterine cavity after **B-Lynch suture**. (Goojha et al. 2010 Fertil Steril)
- 7/13 patients (**54%**) had intrauterine synechia at **hysteroscopy**, following uterine compression sutures for postpartum haemorrhage. (Rathat et al. 2011 Fertil Steril)
- Major intrauterine synechiae, absence of endometrium, and ovarian function failure following **uterine devascularization**. (Roman et al. 2005 Fertil Steril)



Which patients develop intrauterine adhesions?

pregnancy

- Out of 1856 women with intrauterine adhesions, 67% had undergone curettage because of abortion, and 22% because of postpartum hemorrhage (Schenker & Margalioth 1982)
- **Physiologic changes** could make the gravid uterus more vulnerable after pregnancy, making the basal layer of endometrium more easily damaged by any trauma, especially curettage. (Yu et al. 2008)
- The **low estrogen status** at the time of the operation or immediately afterward as a co-factor; as the endometrium depends on estrogen for regeneration. (Yu et al. 2008)

pregnancy

- **Retained products** of conception/placenta (fibroblast activity? infection?)
- **Post-partum haemorrhage** is a risk factor for intrauterine adhesions, with possible contributing factors such as postpartum uterine **instrumentation** or fibrosed **retained products** of conception that may have caused the pathological bleeding.

recurrent miscarriage

- The finding of IUA is commoner in patients with recurrent miscarriage.
- **18.8%** after first abortion vs **47.6%** in patients with recurrent abortions. (Römer T. 1994)
- **16.3%** following only one abortion, **14%** after two abortions, and **32%** after three or more spontaneous abortions ($P < 0.05$) (Friedler et al. 1993)
- In addition, adhesions after two or more abortions are of a **more severe extent**. (Friedler et al. 1993)
- **Cause or Effect?**

mullerian anomalies

- Association between mullerian duct malformations and Asherman syndrome in infertile women. (Stillman RJ, Asarkof N. Obstet Gynecol. 1985 May;65(5):673-7).
- Predisposed to miscarriages and related D&Cs.
- Higher risk of trauma after D&C due to anatomy.

infection

- The role of infections is **controversial** as a causative factor of intrauterine adhesions. (Yes: Czernobilsky, 1978; Taylor, 1981. No: Polishuk, 1975)
- Still, endometritis is often **undiagnosed**: Hysteroscopy identifies endometritis in 13% of patients with repeated failure of IVF-ET, none of them suspected at standard TV ultrasound (Oliveira et al. 2003)

infection

- It seems reasonable to hypothesize that infection, **as any other inflammatory process**, might contribute to the damaging effect of surgical trauma and promote the development of intrauterine adhesions.
- Moreover, infection has been described as a causative factor alone (**septic abortion**, Megafu 1990; **tuberculosis**, Sharma 2008; **schistosomiasis**, Krolikowski 1995)

genetic / systemic factors?

- It is commonly believed that certain patients have an individual predisposition to the development of adhesions.
- No differences in intra-abdominal adhesions among patients of different races, but higher rate of postsurgical adhesions in women with **keloids**. (Tulandi et al. 2011, AJOG)
- This might explain recurring adhesions or adhesions without plausible causative factors.

Conclusions

Conclusions

- Postoperative intrauterine adhesions represent a possibly underestimated complication of intrauterine and transmural surgery.
- The etiology of adhesions is probably multifactorial but their mechanism is still largely unknown.
- Trauma to the basal layer of the endometrium is a key factor, which promotes healing through repair instead for tissue regeneration.
- Hypoxia
- Diagnostic pitfalls can justify a relative under-reporting of intrauterine adhesions

Conclusions

- Trauma to the post-pregnant uterus is the main cause of intrauterine adhesions, although they can also occur after surgery on non-pregnant uterus.
- Although the mechanisms of adhesions are not fully understood, current knowledge indicates which interventions and individual conditions have a higher adhesiogenic potential.
- Extent of trauma, number of procedures, instruments
- Pregnancy, hypoestrogenism, infection, genetic factors?
- Surgeons should use that knowledge to prevent adhesions, do an early diagnose, and correctly counsel patients.

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HYSTEROSCOPIC TREATMENT OF ASHERMAN SYNDROME

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Declaration of interest : None

Learning Objective

- To understand the definition, causation and diagnosis of Asherman Syndrome
- To provide an update on the techniques used in hysteroscopic treatment of intra-uterine adhesion
- To discuss how to avoid complications resulting from hysteroscopic adhesiolysis
- To examine new methods in prevention of adhesion reformation after surgery
- To review the outcome & prognosis of hysteroscopic Adhesiolysis
- To formulate strategies to prevent Asherman syndrome

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Definition

■ Original description:

A consequence of trauma to the endometrium, producing partial or complete obliteration in the uterine cavity, and / or the cervical canal, resulting in conditions such as menstrual abnormalities and infertility.

Prevalence

Infertile women

| Authors | No. of cases | No. of AS | Rate |
|----------------------------|--------------|-----------|-------|
| Taylor et al. | 235 | 48 | 21.4% |
| Stillman and Asarkof. | 537 | 26 | 4.8% |
| La Sala et al. | 100 | 6 | 6% |
| Nawroth et al. | 379 | 26 | 6.9% |
| Preuthipans and Linasmita. | 336 | 74 | 22.0% |
| Yucebilgin et al. | 115 | 2 | 1.7% |
| Hinckley and Milki. | 1000 | 30 | 3% |
| Total | 2702 | 212 | 7.8% |

Etiology

- **Trauma to a gravid uterine cavity postpartum or after a miscarriage**
- **Trauma to non-gravid endometrium**
- **Infection**
- **Congenital anomaly**
- **Genetic predisposition**

Pathology

Asherman syndrome is characterised by endometrial fibrosis

Symptomatology

- **Menstrual abnormalities**
- **Infertility**
- **Recurrent pregnancy loss**
- **Late pregnancy complications**

DIAGNOSIS

The diagnosis of Asherman syndrome should be based on:

1. one or more clinical symptoms: amenorrhea, hypomenorrhoea, subfertility, recurrent pregnancy loss, history of premature labour
2. the presence of intrauterine adhesions or intrauterine fibrosis

Investigations

- **HSG**
- **Ultrasound**
- **Hysterosalpingo-contrast-sonography (HyCoSy)**
- **MRI**
- **Hysteroscopy**

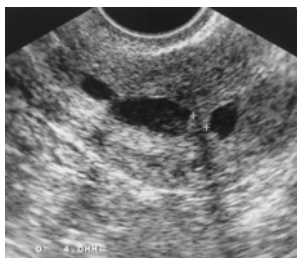
Hysterosalpingography
in women with Asherman`s syndrome



Diagnosis of intra-uterine
adhesions

- HSG may show characteristic features, but it may be 'normal'. Sometimes, the only clue is a report saying that 'the cavity is a little small' which may signify marginal adhesions

Transvaginal ultrasonography



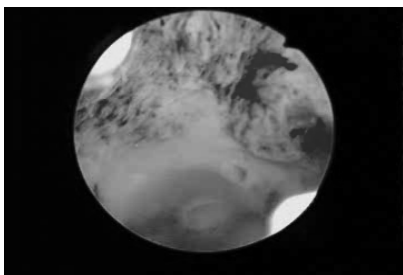
Diagnosis of intra-uterine adhesions

- Ultrasound may show characteristic features in severe cases. Sometimes the only clue is a thin or poorly defined endometrial echo. The ultrasound may be normal especially if the adhesion is located in the isthmic region.

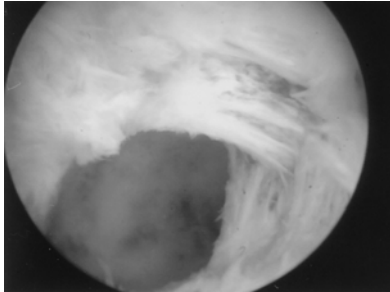
Diagnosis of intra-uterine adhesions

- The diagnosis may frequently be missed
- The gold standard is hysteroscopy

Subtle adhesions may often be missed



Subtle adhesions may often be missed



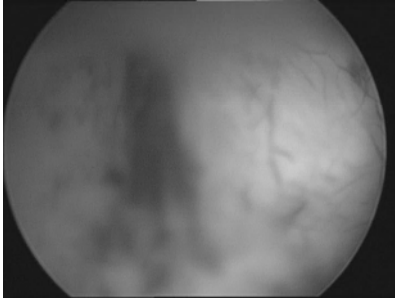
Diagnosis of intra-uterine adhesions

- Even with hysteroscopy, the diagnosis may be missed by a relatively in-experienced surgeon

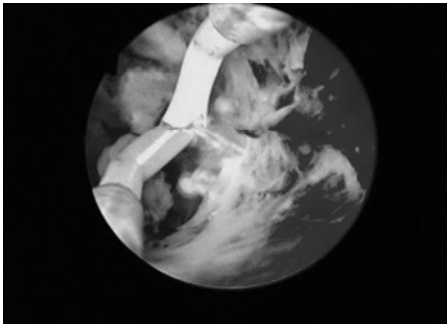
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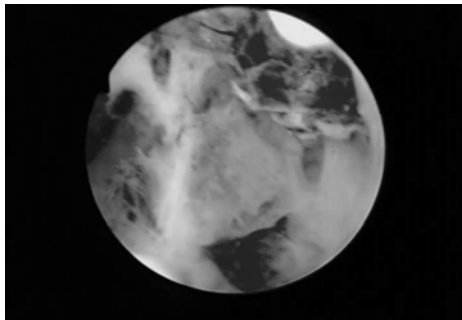
Intrauterine adhesiolysis
(scissors)



Pointed diathermy



loop



Hysteroscopic adhesiolysis

use different techniques for adhesions at different locations

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Complications of hysteroscopic adhesiolysis

- Perforation of the uterus
- Haemorrhage
- Recurrence of adhesions

**Perforation during hysteroscopic
adhesiolysis for Asherman syndrome**

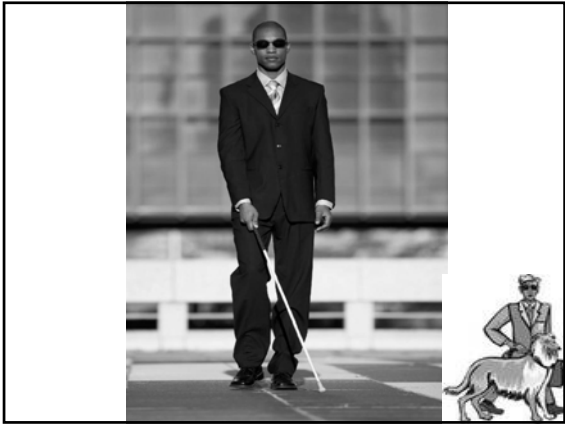
| Authors | All cases | | Severe cases | |
|-----------------------|------------|------------------|--------------|------------------|
| | Number | Perforation | Number | Perforation |
| Valle and Sciarra | 187 | 5 (2.7%) | 47 | 3 (6.4%) |
| Pabuccu et al. | 40 | 1 (2.5%) | 10 | 1 (10%) |
| Feng et al. | 365 | 4 (1.1%) | 39 | 4 (10.3%) |
| McComb and Wagner | - | - | 6 | 3 (50%) |
| Broome and Vancaillie | - | - | 55 | 2 (3.6%) |
| Capella-Allouc et al. | - | - | 31 | 4 (12.9%) |
| Total | 592 | 10 (1.7%) | 188 | 17 (9.0%) |

Recurrent of adhesions

| Authors | All cases | | Severe cases | |
|----------------------------|------------|-------------------|--------------|----------------------|
| | Number | Reformation | Number | Reformation |
| Valle and Sciarra | 187 | 44 (23.5%) | 47 | 23 (48.9%) |
| Pabuccu et al | 40 | 8 (20%) | 10 | 6 (60%) |
| Capella-Allouc et al. | - | - | 16 | 10 (62.5%) |
| Preutthipan and Linasmita. | 65 | 2 (3.1%) | 10 | 2 ^a (20%) |
| Total | 292 | 54 (18.5%) | 83 | 41 (49.4%) |

How to avoid complications?

Perforation of the uterus



*Hysteroscopic Adhesiolysis
Methods of Guidance*

- X-ray control

*Hysteroscopic Adhesiolysis
Methods of Guidance*

- X-ray control
- Laparoscopy

***Hysteroscopic Adhesiolysis
Methods of Guidance***

- X-ray control
- Laparoscopy
- **Trans-abdominal ultrasound**

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***Prevention of recurrence of
adhesion***

- Antibiotic therapy
- Promote regeneration
- Intrauterine contraceptive device (IUD) or intra-intrauterine balloon
- Hyaluronic acide (HA)

Promote regeneration

■ Estrogen therapy

Oestradiol valerate 6mg daily for 6 weeks
Provera 10mg tds weeks 5 & 6

■ Stem cell therapy

Intrauterine contraceptive device (IUD)

■ Keep the raw, dissected surfaces separated during the initial healing phase

Massouras HG. 1973
Jewelewicz et al. 1976
Polishuk et al. 1976
San Fillippo et al. 1982
Shaffer W. 1986

Foley balloon catheter

■ Maintenance of the freshly separated cavity by separating the opposing uterine walls

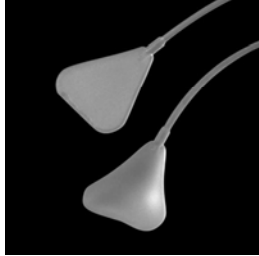
■ Infection from the vagina

■ Over-inflated balloon will increase pressure on the uterine walls which might result in decreased blood flow to uterine walls affecting endometrial regeneration.

■ Produce significant discomfort.

Klein SM and Garcia C-R. 1973
Orhue AA, et al. 2003

Specially designed Intra-uterine balloon

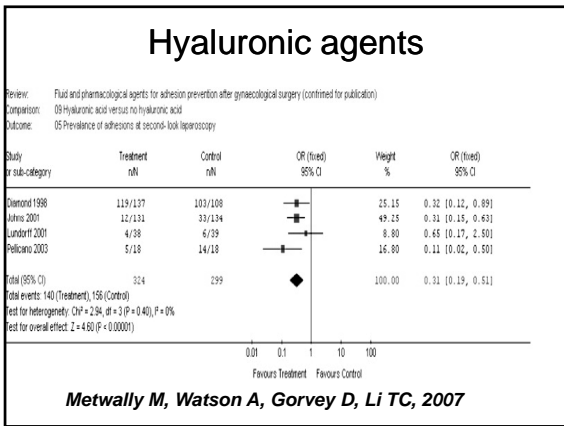


- Inflate the balloon with 5 or 8 ml of saline
- Keep balloon in uterine cavity for 5 -7 days
- Antibiotic for as long as balloon is in
- If there is significant pain, may reduce the volume of fluid in balloon
- Remove balloon as an outpatient procedure after deflation the balloon

Hyaluronic acide (HA)

- a barrier agent to prevent adhesion development after surgery.
- Auto-cross-linked HA (ACP) gel (Hyalobarrier gel, Baxter, Pisa, Italy)

Tsapanos VS, et al. 2002; Acunzo G, et al. 2003; Guida M, et al. 2004



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- ### Outcome of treatment
- Restoration of normal anatomy of the uterine cavity.
 - Restoration of normal menses.
 - Pregnancy rate and live birth rate (in women presented with infertility or pregnancy wastage).

Restoration of menstruation in women presenting with amenorrhea or hypomenorrhea

| Authors | Number of cases | Normal menses following surgery, Number (%) |
|--------------------------|-----------------|---|
| Fedele et al | 21 | 11 (52.4%) |
| Valle and Sciarra | 169 | 149 (88.2%) |
| Pabuccu et al | 34 | 29 (85.3%) |
| Feng et al | 351 | 294 (83.8%) |
| Preuthipan and Linasmita | 50 | 45 (85%) |
| Total | 625 | 528 (84.5%) |

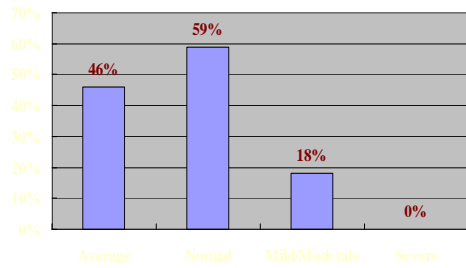
Women with infertility

| Authors | All cases | | | Severe cases | | |
|---------------------------|-----------------|--------------------|-------------------------|--------------|-------------------|------------------|
| | No. | conception | live birth | No. | conception | live birth |
| Valle and Sciarra | 81 | 48 (59.2%) | 29 (35.8%) | 30 | 13 (43.3%) | 5 (16.7%) |
| Pistofidis et al. | 86 ^a | 30 (34.9%) | 21 ^b (24.4%) | 11 | 3 (27.3%) | 0 |
| Pabuccu et al. | 16 | 10 (62%) | 6 (37.5%) | 4 | 0 | 0 |
| Preuthipan and Linasmita. | 45 | 16 (35.6%) | 16 (35.6%) | 10 | 2 (20%) | 2(20%) |
| Total | 228 | 104 (45.6%) | 72 (31.6%) | 55 | 18 (32.7%) | 7 (12.7%) |

women with pregnancy loss

| Authors | All cases | | | Severe cases | | |
|---------------------------|------------|--------------------|--------------------|--------------|-------------------|-------------------|
| | No. | conception | live birth | No. | conception | live birth |
| Valle and Sciarra | 106 | 95 (89.6%) | 85 (80.2%) | 17 | 14 (82.3%) | 11 (64.7%) |
| Pabuccu et al. | 24 | 24 (100%) | 17 (70.8%) | - | - | - |
| Preuthipan and Linasmita. | 5 | 2 (40%) | 2 (40%) | - | - | - |
| Total | 135 | 121 (89.6%) | 104 (77.0%) | 17 | 14 (82.3%) | 11 (64.7%) |

The relationship between conception rate and second look hysteroscopy



- The conception rate after treatment - 46% (39/85).
- Good prognosis:
 - normal period after the procedure
 - normal uterine cavity at second look hysteroscopy
- Bad prognosis:
 - hypo/amenorrhea after treatment
 - recurrence of adhesions

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- To review the outcome & prognosis of hysteroscopic Adhesiolysis
- To formulate strategies to prevent Asherman syndrome

Prevention of Asherman syndrome

- Avoid post-partum curettage
- Gentle curettage
- Medical management of miscarriage

**Intra-uterine surgery
Methods of guidance**

1. Hysteroscopic
2. Ultrasonographic
3. Combined

Termination of pregnancy

Ultrasound guidance

**Stop the surgery when the
cavity is empty!**

There is no need to do check
curettage

Retained product of conception

Hysteroscopic guidance

Hysteroscopic guided removal of retained product of conception if it is more than 2 weeks old

Difficult or Advanced intra-uterine surgery

e.g. Delayed miscarriage in a women with a fibroid ditorting the cavity

Combined Ultrasound and hysteroscopic guidance

Case History 1

- 24 year old women
- unplanned pregnancy, requested termination
- Bleeding continued for 2 weeks
- Ultrasound showed ?retained product
- Had a second evacuation procedure
- Scanty periods afterwards
- Infertile for 2 years
- Diagnosis – severe Asherman syndrome (intrauterine adhesions), attempted hysteroscopy resulted in perforation of uterus

Case History 2

- 32 year old doctor, normal delivery at 40 weeks
- Heavy bleeding 2 weeks puerperium
- Ultrasound retained piece of placental tissue
- Evacuation – little tissue obtained
- Bleeding persisted
- Repeated ultrasound – product of conception still visualised
- Hysteroscopy under ultrasound guidance – placental tissue embedded in posterior wall
- Conservative measures with antibiotics & progestogen, tissue gradually absorbed

Debate

Surgical termination of pregnancy or evacuation of retained product of conception should nowadays be routinely performed under ultrasound guidance

Reduce Damage due to Infection

- Aseptic techniques
- Pre-operative infection screen
- Antibiotic cover

Summary 1

- **Diagnosis** – diagnosis may often be missed, gold-standard is hysteroscopy
- **Treatment** – hysteroscopic adhesiolysis by using scissors or diathermy, dependent on the exact location of the adhesions
- **Complications** - Ultrasound guidance is mandatory
- **Strategies to prevent recurrence of adhesions** including the use of intra-uterine balloon

Summary 2

- **The prognosis depends on recurrence of adhesions at second look hysteroscopy**
- **Asherman syndrome is a preventable condition**
- **Close surveillance of the pregnancies after treatment is essential as a number of obstetrics complications may occur.**
- **The focus of future research should be on the prevention of post-surgical adhesion reformation**

Thank You

Prevention of postoperative intra uterine adhesions

European
theAcademy of
Gynaecological
Surgery

Rudi Campo, MD
Leuven Institute for Fertility and Embryology
LIFE
Leuven - Belgium

Disclosure

Karl Storz endoscope GmbH, Tuttlingen, Germany
Licensor and consultant

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Prevention of post operative intrauterine adhaesions.

The variable nature of this condition, the multitude of classification systems, management approaches and varying methods for measuring outcome results provides a condition of poor scientific evidence on any statement.

Any event that causes damage to the basal endometrial layer may lead to development of intrauterine adhesions but it is often seen as a dialogue between a definable causative event and an unknown predisposing factor.

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Predisposing factors

- **Individual predisposition**
Different reaction to same trauma and treatment.
Adhesions formation is reported even in the absence of any attributable trauma.
- **Gravid uterus - Retained placental remnants**
Among the 1856 cases of Asherman syndrome reviewed by Schenker (1982), pregnancy was the dominating predisposing factor (90.8%)
Reason ? : Low oestrogen status, physiologic or pathophysiologic changes occur in a gravid uterus making the basal layer of endometrium more easily damaged by any trauma?
- **Infections ?**
Its role is still controversial.
- **Breast-feeding**
Women who nurse remain estrogen deficient for a prolonged period and thus the stimulus to endometrial regeneration is missing.

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Causative factor

- **Surgery**
Post-partum or post-abortion dilatation and curettage
Operative hysteroscopy
Uterine surgery (e.g. caesarean section, myomectomy)
- **Pelvic irradiation and uterine embolisation**
- **Infections**
Genital infections like tuberculosis, endometritis, puerperal and post-abortion sepsis.
Chronic inflammation of the endometrium.

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How can we prevent post operative intrauterine adhaesions ?

Strategy in the pregnant uterus.

Modern approach to uterine diagnose and surgery.

Instrumentation ?

Surgical technique in high risk pathology.

Ancillary treatment ?

Hyaluronic acid derivative adhesion barrier ?

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Manipulation in Pregnant Uterus
High Risk procedure for adhaesion formation

D&C for miscarriage and D&C or surgery for placental remnants provides the highest risk for intra uterine adhaesion formation. (21 - 66 %)

Repeated D&C because of miscarriage have an increased incidence of intra uterine adhaesions (14 - 40 %)

Deans R, Abbott J. Review of intrauterine adhesions. J Minim Invasive Gynecol 2010 Sep-Oct;17(5):555-69.
C.Nappi et al. Prevention of adhesions in gynaecological endoscopy, Human Reproduction Update, Vol.13, No.4 pp. 379-394.



Strategy in the pregnant uterus

Non surgical management of incomplete miscarriage produces less adhaesions than a D&C

A sharp curette tends to produce more adhaesions than a blunt or a suction curette.
Suction curette can be advised.

Remnants after D&C should always be treated hysteroscopically under US guidance.



Hysteroscopic surgery of pregnancy remnants

Aim of the surgery is to reconstruct the intrauterine anatomy

Surgical steps .

1. Remove all intracavitary tissue.
2. Resect the intramyometrial cicatricial area
3. Correct if possible concomittant pathology



Hysteroscopic surgery of pregnancy remnants

Surgical technique

- Use preferentially mechanical energy, then bipolar rather than unipolar.
- Remove carefully the intracavitary necrotic tissue mechanically with 5 French instruments or resectoscope cold resection.
- Identify and resects the intramyometrial invasion with the micro scissors, in case of bleeding use the bipolar needle or resectoscope
- Perform surgery under US guidance for intramyometrial exploration and keep safety zone of 5 mm.

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Hysteroscopic surgery how to prevent adhaesions ?

VIDEO DEMONSTRATION

Hysteroscopic removal of pregnancy remnants.

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How can we prevent post operative intrauterine adhaesions ?

Strategy in the pregnant uterus.

Modern approach to uterine diagnose and surgery.

Instrumentation ?

Surgical technique in high risk pathology.

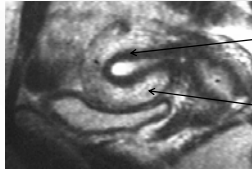
Ancillary treatment ?

Hyaluronic acid derivative adhesion barrier ?

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Non Pregnant uterus functional anatomy

Myometrium has 2 structural and functional different entities seen in MRI



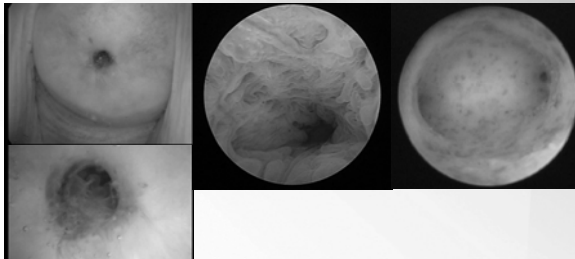
Junctional zone
small central zone of increased density
IMPORTANT IN REPRODUCTION

Outer myometrium
Larger outer hypodenser zone

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Modern Hysteroscopy

Gold standard for intra uterine diagnosis and treatment



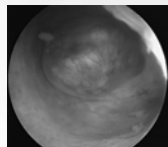
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Modern uterine approach "US-HSC-US"

Should be performed in any case of uterine diagnostics in infertile patients and abnormal uterine bleeding disorders, simultaneous to and as easy as a Trans Vaginal Ultrasound.



Ultrasound



Hysteroscopy



Contrast sonography

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New Tools

Trophy Hysteroscope acc. to Campo

New generation of hysteroscope with interesting characteristics named after the multicentre study TROPHY "Trial of Outpatient Hysteroscopy" for which it was designed.

EI-Toukhy T, Campo R et al. Trial of Outpatient Hysteroscopy – (TROPHY) in IVF. Reprod Health. 2009 Dec; 3:6:20.

Spirotome acc. to Gordts

A device made to harvest high quality samples from soft tissues, built on the pioneering concept of a cutting helix on a cutting cannula.

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Trophy hysteroscope



2,9 mm total diameter single flow compact hysteroscope does not require assembling.

Reduced trauma and smooth passage through cervical canal

- No sticking of tissue to the optic
- Comfortable instrument length and handling
- Increased illumination
- Progressive and atraumatic dilatation.

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Trophy Scope, 2,9 mm compactscope with Innovative gliding mechanism for accessory sheets

Accessory diagnostic sheet can be activated in case of necessity by gently push on the bottom and forward movement till locking in the active position. Creating double flow and blocking of cervix in case of passive outflow to improve visualisation



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Trophy Scope Diagnostic accessory sheet

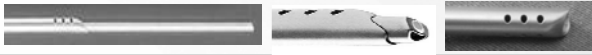
In active position
Atraumatic cervical dilatation up to 3.7 mm under visual control
Creating double flow
Blocking of cervix in case of passive outflow

In free position
Suction device for endometrial sampling
Guide for ultrasound guided intrauterine procedures like positioning Embryo transfer catheter or for Spirotome endomyometrial biopsy and assistance to difficult Asherman Surgery

Passive

Active

Free



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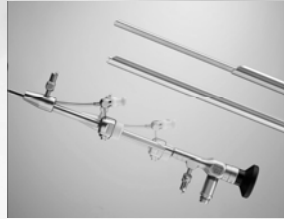
Trophy Scope Operative accessory sheet

In passive position
Operative sheet does not interfere the diagnostic phase (2,9mm).

In active position
Atraumatic cervical dilatation up to 4,4 mm under visual control

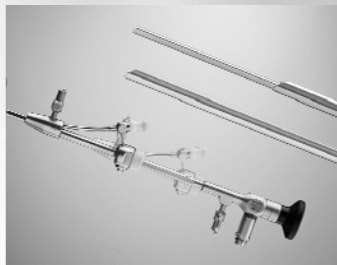
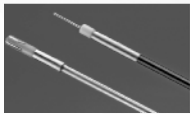
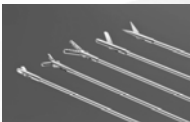
Creating double flow and blocking function in case of passive outflow

Introduction of 5 Fr. instruments without compromising inflow.



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Surgery with Trophy hysteroscope



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New Tools for Myometrial Exploration

Spirotome acc. to Gordts

A device made to harvest high quality samples from soft tissues.

It is built on the pioneering concept of a cutting helix on a cutting cannula well identified by Ultrasound.



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Spirotome use through diagnostic sheet

The Trophy hysteroscope can be removed leaving the continuous flow in place, can be used as an atraumatic guide for the Spirotome.



Indication

Myometrial biopsy to confirm adenomyosis

Asherman syndrome creating pathway to the endometrial area in the cornua.

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Hysteroscopic surgery how to prevent adhaesions ?

VIDEO DEMONSTRATION

Use of Spirotome under US guidance

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Modern Hysteroscopic Surgery.

- As for all surgical interventions, an appropriate hysteroscopic surgical technique with minimal tissue damage and anatomical responsible approach, may minimize the risk of post-operative intra uterine adhaesions.
- General recommendations include avoiding trauma of healthy endometrium and myometrium surrounding the lesions to be removed, reducing the usage of electro-surgery whenever possible (Chen et al., 1997) especially during the removal of myomas with extensive intramural involvement (Mazzon, 1995) and avoiding forced cervical manipulation.
- First data comparing monopolar and bipolar electro-surgery on postoperative IUA suggest less adhaesion formation using bipolar energy.

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Reported Incidence of adhesion formation after trauma to the non pregnant uterus

| | |
|--------------------------------|--------|
| D&C: | 1,6 % |
| POLYPECTOMY : | 0,5 % |
| IUD : | 0,2 % |
| SEPTUM DISSECTION : | 6,7 % |
| SINGLE MYOMA : | 31,3 % |
| ENDOMETRIAL BALLOON ABLATION : | 36,4 % |
| MULTIPEL MYOMA : | 45,5 % |
| ASHERMANN SURGERY : | 41,9 % |
| ADENOMYOSIS: | ?? |

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Deans R, Abbott J. Review of intrauterine adhesions. J Minim Invasive Gynecol 2010 Sep-Oct;17(5):555-69.

Hysteroscopic surgery how to prevent adhaesions ?

Myoma surgery

- The literature reports an variable incidence of 7,5 % - 45,5 % of adhaesion formation after hysteroscopic myomectomy. (Taskin et al. 2000, Yang et al 2008, Touboul C et al 2009)
- The discrepancy among different publications originates in the Heterogeneous population samples and the anatomical diversity:
 - Single myoma, apposing myomas, multiple intramural myomas, concomittant adenomyosis ?
 - Different modes of energy, monopolar – bipolar – mechanical.
 - Variable use of GnRH analogue pre treatment.

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Hysteroscopic Myomectomy

Surgical technique

- Surgery only under clear vision
- Coagulation of major vessels
- Concomitant ultrasound or laparoscopy available
- Intramural resection without destroying the surrounding myometrium
minimal myometrial safety margin of 5 mm

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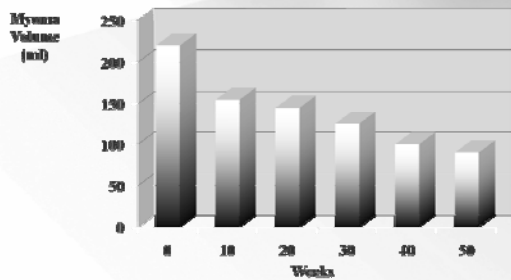
Reducing operative risk by GnRH-a therapy ?

AIM

- Induction of amenorrhoea
control any concomitant menorrhagia
correction of pre-operative anaemia
- Reduction size of the fibroid(s)
- Reduction in total uterine volume

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Reduction in volume of the fibroids?



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Combined medical - surgical approach



GnRH-a treatment should be phase one of a two-phase treatment plan for uterine fibroids followed by surgery

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A. Golan, Hum Reprod. 1996

Combined medical - surgical approach

Indications

Myoma larger than 2 cm

Anaemia

Relative Indications

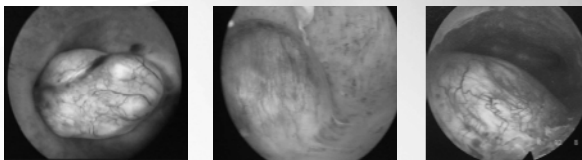
More than one sub-mucous myoma

Myoma localisation

Endometrial vascularisation

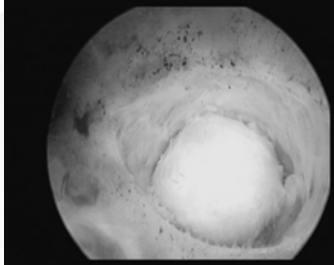
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Hysteroscopic Myomectomy



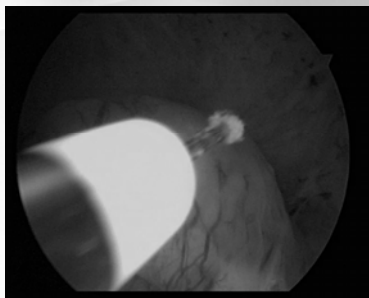
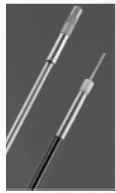
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5 French microscissors



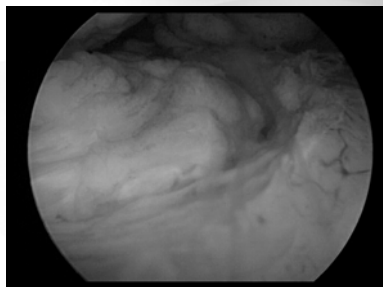
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5 French Bipolar probes



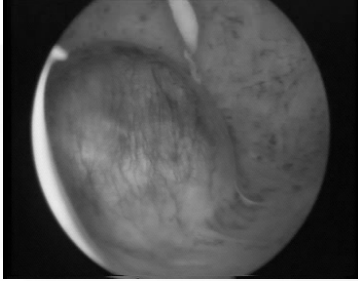
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5 French Bipolar probes



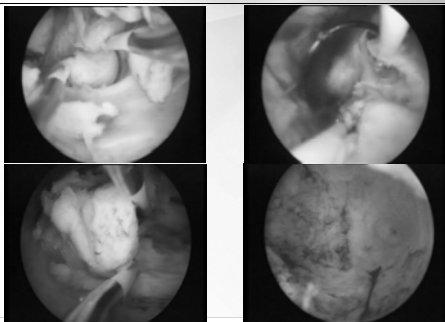
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Unipolar myoma Typ 1 resection



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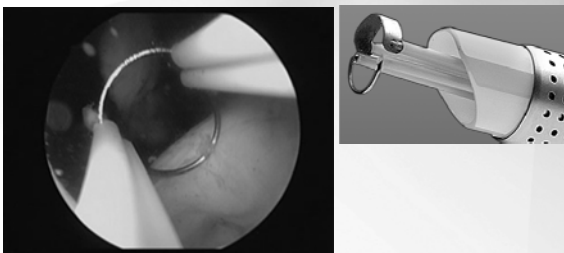
Unipolar myoma Typ 1 resection



theAcademy

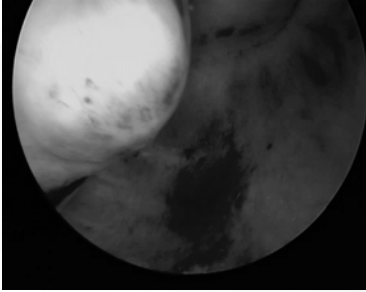
Bipolar resectoscope for myoma

Ionic fluid



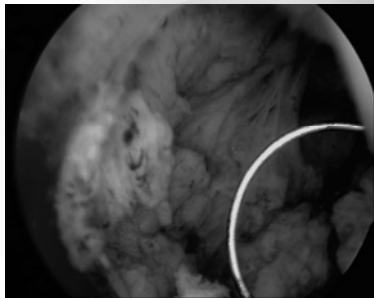
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Bipolar myoma Typ 2 resection



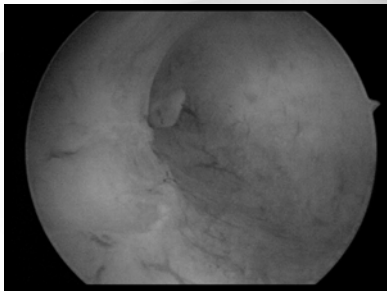
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Bipolar myoma Typ 2 resection



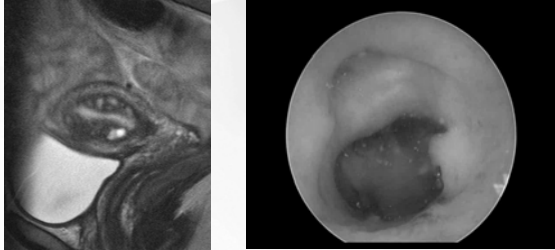
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Resection of adenomyoma



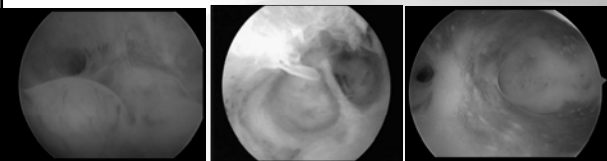
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Postoperative Result.



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Treatment of Ashermann Syndrome.



VIDEO DEMONSTRATION

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Operative Hysteroscopy overview.

| 2007-2010 | N interventions | Postoperative adhaesions | Remarks |
|----------------------|-----------------|--------------------------|--|
| Polypresection | 433 | < 5 % | |
| Myomectomie | 149 | < 5 % | 1 after embolisation 1 adenomyosis |
| Uterusplastie/septum | 183 | < 5 % | Only large septa in fundal area |
| Endometriumresection | 197 | Not validated | |
| Ashermann | 50 | 32 % | High for grade 3 and 4 |
| Placental remanants | 62 | 5 - 10 % | Increases with use of monopolar resectoscope |
| Total | 1074 | | |

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R. Campo non published data

How can we prevent post operative intrauterine adhaesions ?

Strategy in the pregnant uterus.

Modern approach to uterine diagnose and surgery.

Instrumentation ?

Surgical technique in high risk pathology.

Ancillary treatment ?

Hyaluronic acid derivative adhesion barrier ?

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Rational- Hyaluronan: chemistry

Hyaluronan is a naturally occurring, biocompatible and biodegradable linear polysaccharide composed of repeating monomeric units of N-acetyl glucosamine and D-glucuronic acid.

Ancient molecule- identical from bacteria to man

Biocompatible, Highly hygroscopic with excellent safety profile

Found in ECM of major connective tissues (skin, cartilage etc....)

Involved in tissue repair and regeneration

- Quickly cleared
- Inadequately viscous
- Low residence time

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Yarali H J Reprod Med 1994;39:667-670, Hill-West J Fertil Steril 1994;62:630-4
Burns JW Surg Res 1995;59:644-52, Urman B Fertil Steril 1991;56:563-7

Hyalobarrier®: Increased viscosity

•A hyaluronan auto-crosslinked polymer (ACP® gel) is obtained by a condensation reaction between hyaluronan carboxyl and hydroxyl groups (inter and intramolecular links) without the use of any foreign bridge molecules. Viscosity and residence time increases

- Hydration of ACP® generates a highly viscous gel, Hyalobarrier®
 - same safety profile of HA (same degradation pathway)
 - longer residence time than pure HA (bio-absorbable within 7 days)
 - Can be used in laparotomy, laparoscopy and hysteroscopy
 - Effective in adhesion prevention

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Cellular activity of scar formation

| Time after surgery | What is happening |
|--------------------|--|
| Immediately | Inflammation causes the macrophages, fibroblasts and fibrin matrix to move the surface of the wound. |
| Day 3 | - Macrophages form the foundation of the advancing adhesions; - Proliferation of fibroblasts and vasculisation result in fibrin matrix advancement. |
| Day 5 | Scars are increasing in vascular and organised in structure. |
| Day 7 | No new scar formation. |

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Hyalobarrier®: Scientific evidence

- ACP® gel significantly reduces the incidence and severity of de-novo formation of intrauterine adhesions after hysteroscopic surgery.

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;18:1918–21.

Effectiveness of auto-crosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: a prospective, randomized, controlled study. M. Guida et al. Hum Reprod 2004;19:1461–4.

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Other adjuvant therapies to prevent adhaesions ?

| | |
|-------------------------------|---|
| Antibiotics | No scientific evidence Routine doxy 200 mg for 10 days |
| Oestrogen therapy | controversial, advise is to supplement in women with no ovulatory cycle or under GnRH analogue treatment. |
| Mechanical barrier | Evidence that it does not help |
| Repetitive HSC control | Interesting idea With new instruments feasible When and how frequent ? |

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Conclusion 1
Hysteroscopic surgery how to prevent adhaesions ?

The pregnant Uterus

- Prefer non surgical management of incomplete miscarriage.
- Prefer a suction curette above the blunt or sharp curette.
- Always perform a combined hysteroscopic – US guided procedure to remove residual pregnancy tissue
- Prefer mechanical Instrumentations above bipolar and monopolar energy.



Conclusion 2
Hysteroscopic surgery how to prevent adhaesions ?

The non pregnant Uterus

- Modern approach to uterine diagnosis and treatment is a combination of US and hysteroscopy.
- The Trophy scope provides a new approach for minimal invasive US guided hysteroscopic surgery. Especially the use of the Spirotome opens interesting pathways for Ashermann surgery.
- Myoma surgery and Ashermann surgery have the highest post operative incidence of adhaesion formation.




Conclusion 3
Hysteroscopic surgery how to prevent adhaesions ?

The non pregnant Uterus

- Whereas minimal invasive surgery with respect to the anatomy can prevent adhaesion formation in myoma surgery, supplementary help is needed in case of severe Ashermann, post embolisation surgery or adenomyose surgery.
- Hyalobarrier® is a natural anti adhaesive agent which is registered for intra uterine application.
- Scientific evidence is provided that application of Hyalobarrier® reduces the incidence and severity of adhaesion formation.





Endoscopy Courses 2008


+theAcademy

More info on the training programmes in endoscopic surgery:


info@theacademy house.org
www.theacademy house.org

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Leuven Institute for Fertility & Embryology



Rudi Campo
Stephan Gordts
Patrick Puttemans
Roger Molinas
Sylvie Gordts
Marion Valkenburg
Ivo Brosens



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Adhesion formation after ovarian drilling
Comparison between laparoscopy and
fertiloscopy

A. Watrelot
Hôpital NATECIA
Lyon
France

OVARIAN DRILLING(for infertile patients)



Criteriae of Rotterdam 2003

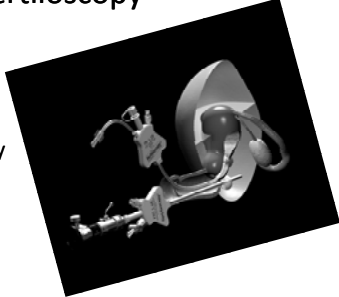
Evolution

- Wedge resection per laparotomy
- Laparoscopic wedge resection
- Laparoscopic ovarian drilling
- Fertiloscopic ovarian drilling



fertiloscopy

1. Hydropelviscopy
2. Dye test
3. Salpingoscopy
4. Microsalpingoscopy
5. hysteroscopy

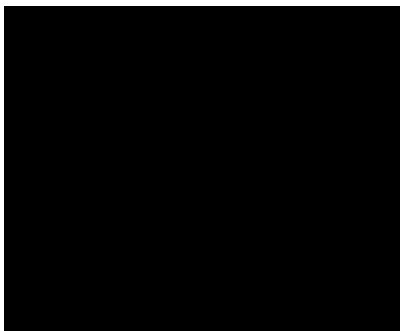


Watrelet et al. Human Reprod 1999

technique



technique



Ovarian drilling: why is it controversial?

- How it works?
- Risks of adhesion formation
- Invasive
- Risk of premature ovarian failure

**Ovarian drilling per
fertiloscopy:TECHNIQUE**

- HYDROPELVISCOPY(step 1)
- Visualization of ovarian ligament
- Bilateral drilling (4-8 holes by side)using bipolar electrocautery)
- Step 2 to 5
- Saline solution is left in place
- New option= ADEPT™

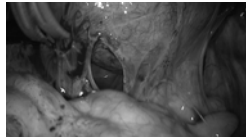
Ovarian drilling in:

- PCO syndrome

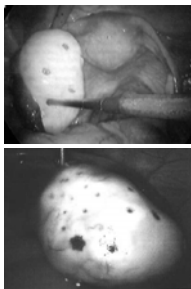


Comparison of ovarian drilling

- Laparoscopy:
 - -monopolar
 - -risk of adhesions
- Fertiloscopy
 - -bipolar
 - -no adhesions



Per laparoscopy

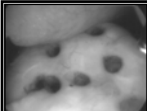


Risk of ovarian failure



| | Patientes | Taux de cycles ovulatoires | Taux de grossesse spontan ¹² | Taux cumul ¹² de grossesse |
|--|-----------|----------------------------|---|---------------------------------------|
| Laparotomie R'sec Z'eun'iforme | 679 | 81,6 (53-94) | 50 (0-5) | 55,3 (12-85) |
| Coelioscopie Electrochirurgie | 720 | 79,7 (30-100) | 51,5 (20-88) | 63,6 (20-88) |
| Coelioscopie Laser | 322 | 71,5 (61-100) | 43,7 (0-75) | 53,1 (0-75) |
| Coelioscopie Biosies/Zon'zec | 82 | 82,6 (73-94) | 48,7 (42-57) | 55 (50-58) |
| Total patientes | 1803 | 1007 | 891 | 1055 |
| Taux globaux | | 78,1 | 49,4 | 58,5 |

¹² Méta-analyse de Campo, 1998



Fertiloscopic ovarian drilling

| | N | pregnancy | delay |
|----------------|----|----------------|----------------|
| FERNANDEZ | | | |
| WATRELOT 2001 | 23 | 62% | 2,8 months |
| CASA 2003 | 28 | 38% à 3 months | 76% à 6 months |
| SHIBAHARA 2006 | 7 | 5 | |

14

Results

- N=80
- Follow-up=18 months (+/-6.4%)
- Ovulation: 73/80 (=91%)
- Cumulative PR:44/73 (=60%) 44/80(55%)
- Mean time :2,8 (1-11,8) months
- Outcome :8 miscarriages(18%) (no twins or ectopic)

Fernandez, Watrelot et al. AAGL journal 2004

Results(2)

- N=122
- Cumulative pregnancy rate=72 (59%)
- No twins,
- Miscariages= 13 (18%)
- Time to pregnancy =2-8 months (range=4,2)
- N=6 second drilling after pregnancy>1 year of secondary infertility , same criteriae)
- Pregnancy=3 additional pregnancies

watrelot, A, Drevfus JM, EMC 2008

- Evaluation of ovarian adhesion formation after laparoscopic ovarian

drilling by second-look minilaparoscopy ● Mercurio F, Mercurio A, Di Spiezio Sardo A, Barba GV, Pellicano M.

- Nappi C Department of Gynaecology and Obstetrics, and Pathophysiology of Human Reproduction, University of Naples Federico II, Naples, Italy, fmercurio@libero.it

- N=90
- adhesions=54 (60%)
- Independent of the number of holes


SECOND LOOK

| | N | filmy adhesions | connective adhesions | no adhesions |
|----------------------|----|-----------------|----------------------|--------------|
| 2n OD / tiloscopy | 13 | 5 | 0 | 8 |
| 2n / tiloscopy | 8 | 0 | 0 | 8 |
| 2nd paroscop | 11 | 3 | 1 | 7 |
| total | 32 | 8(25%) | 1 | 23(71,9%) |

no. of filmy adhesions=96,9%

conclusions


- Ovarian drilling per fertiloscopy has in itself some advantages: mini-invasiveness, lack of major risks,efficacy
- Compared to laparoscopy fertiloscopy is less heavy and give almost no post operative adhesions

 **Surgery without adhesions ?**

Disclosures

- eSaturnus NV, board member & shareholder
- Quality Surgery Fund (F&P, Nordic , eSaturnus)
- Storz AG, licensor

Philippe Koninckx

 **Learning objectives**

- Update on peritoneal cavity physiology
- **Surgery (local inflammation)**
 - is necessary to start the adhesion process
 - Is quantitatively less important
- Peritoneal cavity - acute inflammation
 - enhances adhesions of surgery
 - is quantitatively 20 times more important
- Peritoneal cavity conditioning
 - Decreases/abolishes CO2 resorption and its side effects
 - Decreases postoperative pain by >50%
 - Decreases adhesion formation by 70-80%
- Prevention of adhesions
 - First peritoneal cavity conditioning
 - Then consider a barrier
 - ... and achieve over 90% reduction

The peritoneal cavity

• **Cavity lined by a mesothelium**

- on a Basal membrane
- Below fat – vessels

• = 'outside' the body

• A specific micro-environment different from blood

• **Functions of mesothelium**

- Gliding of bowels ,lung, heart
- regulates transport
 - Gap junctions/vesicles



Postoperative adhesions

huge clinical need <---> limited use of barriers

Based upon effect of silastic membranes

Limited efficacy : 40-50 %

for selected surgeries

Limited data available

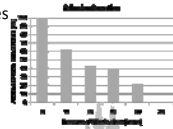
No trials with clinical useful endpoints

fertility

reoperation rate

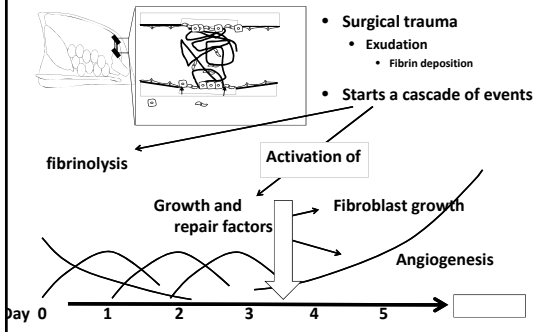
pain

and thus no reimbursement

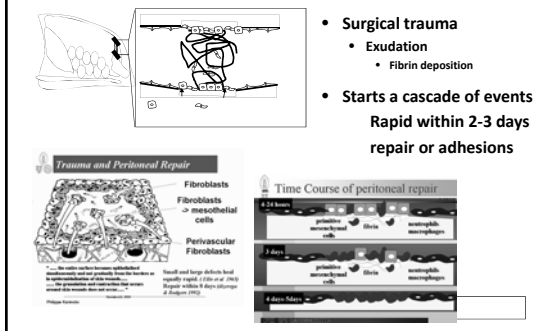


Harris ES, Morgan RJ, Roddeheaver GT.
Analysis of the kinetics of peritoneal adhesion
formation in the rat and evaluation of mechanical
antifibrotic agents.
Surgery 1995;117:663-69

The classic Model : a local phenomenon



The classic Model : a local phenomenon



Adhesion Formation

- **New concepts in adhesion formation**
 - **The abdominal cavity as a cofactor**
 - **Bad = acute inflammation**

Peritoneal cavity is quantitatively 20 times more important than local trauma

Pure surgical Trauma Enhanced by..... All additive

Hypoxia Trauma Desiccation

New concepts in adhesion formation

repair of a surgical lesions is strongly influenced

- **By factors from the entire peritoneal cavity**
 - **Bad = acute inflammation**
 - **Increased by :**
 - mechanical trauma , blood
 - hypoxia, hyperoxia,
 - Desiccation
 - **Decreased by**
 - Lower temperature
 - Dexamethasone
 - New insufflation gaz mixtures

-> **New concepts in adhesion prevention**

The mouse model

Insufflator Heating/humidifier device Water valve Trocar Endoscope Elastic balloon Ventilator

The mouse model

Developed successively by
 Jose Ordonez, Argentina *
 Suren Rampahal, South Africa
 Narter Yesildaglar, Turkey
 Roger Molinas, Paraguay ***
 Ospan Mynbaev, Russia
 Osama Elkilani, Egypt *
 Lloreana Ret Davolos, Argentina
 Mercedes Binda, Argentina ***
 Adriana Bastidas, Ecuador
 Mads Riskjaer, Denmark
 Ron Schonman, Tel Aviv

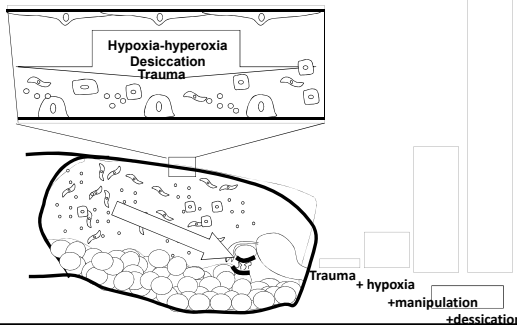
* Master
 *** PhD

Actual program and cooperations
 Karina Mailova, Russia*
 Roberta Corona, Cagliari, Italy ***
 Jasper Verguts, Leuven ***

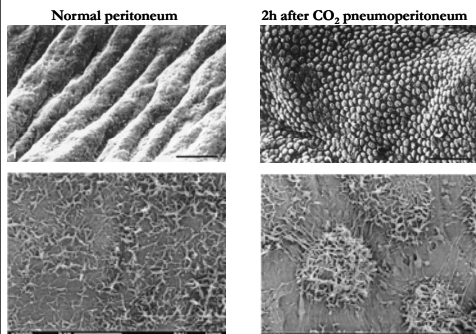
Thomas Koninckx, Leuven, *ESAT -eSaturnus*
 Robert Koninckx, Leuven *eSaturnus*

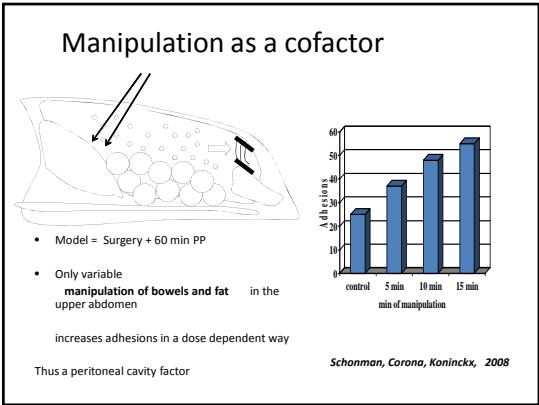
Balbc mice
 Control of ventilation
 Pneumoperitoneum
 pressure duration
 Gaz mixture
 humidification & temperature
 Surgery for adhesion induction
 standardised bipolar lesions
 scoring after 7days (= 60 days)

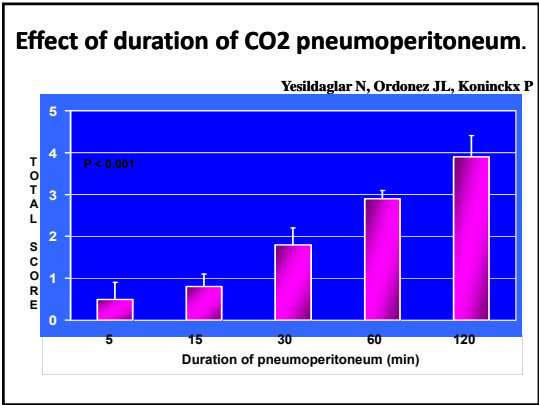
The peritoneal cavity is quantitatively the most important

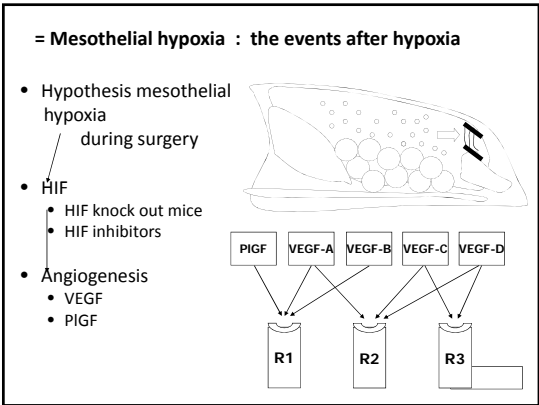


The peritoneal cavity as a co-factor









= Mesothelial hypoxia : the events after hypoxia

Molinas CR and Koninckx PR, Fertil Steril, 2001

- Hypothesis mesothelial hypoxia during surgery
- HIF
 - HIF knock out mice
 - HIF inhibitors
- Angiogenesis
 - VEGF
 - PlGF

Proven in knock-out mice

Normoxia = 4% of oxygen or 28 mm Hg pO2
= minimal amount of adhesions

Hypoxia → HIF → Angiogenesis

hyperoxia → Ros Activity

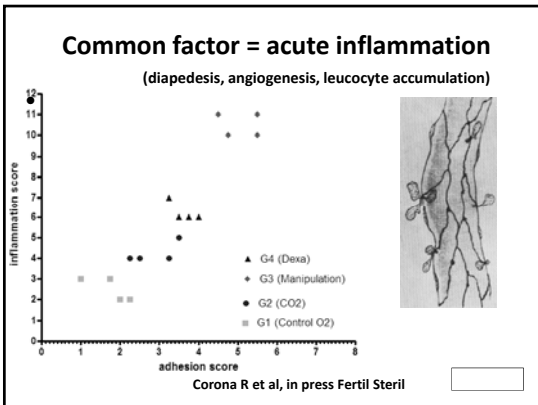
| | | | | | | |
|---|---|----|----|----|-----|-------------|
| 0 | 1 | 2 | 4 | 8 | 16 | % of oxygen |
| 0 | 7 | 14 | 28 | 56 | 112 | pO2 |

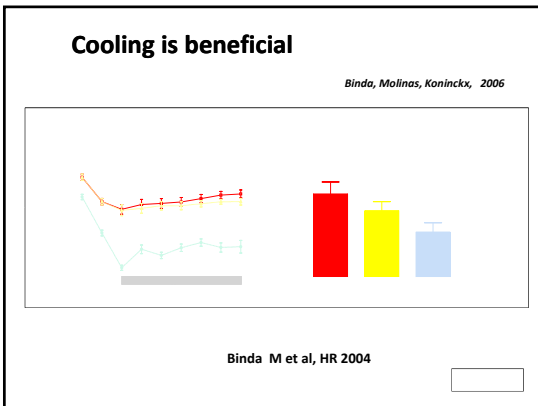
Desiccation increases adhesions

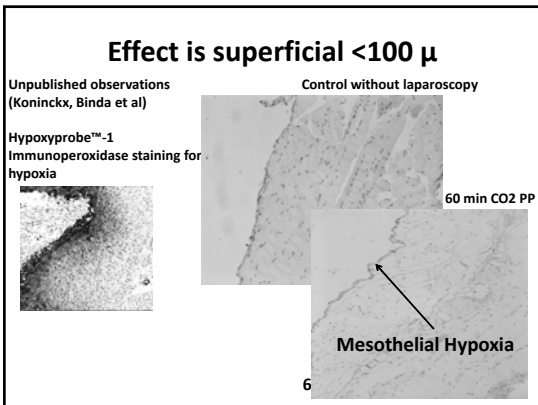
Binda, Molinas, Koninckx, 2006

| Group | Flow (ml/min) | Hum. gas | Hypotermia | Temp during PP | Proportion of adhesions (%) |
|-------|---------------|----------|------------|----------------|-----------------------------|
| I | 0 | No | No | 37.9 ± 0.2 | ~30 |
| II | 23 | No | No | 37.7 ± 0.2 | ~35 |
| III | 100 | No | No | 38.1 ± 0.2 | ~50 |
| IV | 100 | Yes | No | 38.8 ± 0.2 | ~22 |
| V | 100 | No | Yes | 32.7 ± 0.3 | ~25 |

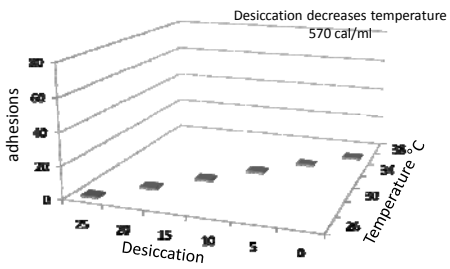
Desiccation



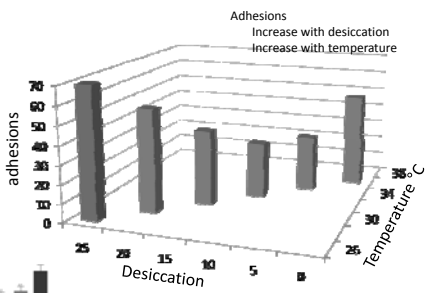




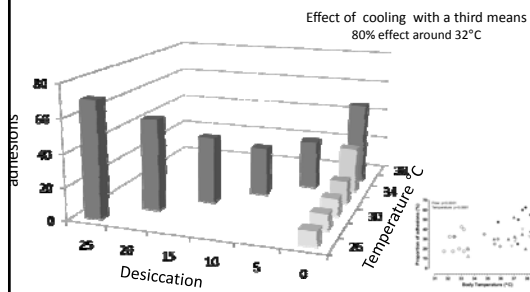
Adhesions – temperature- desiccation

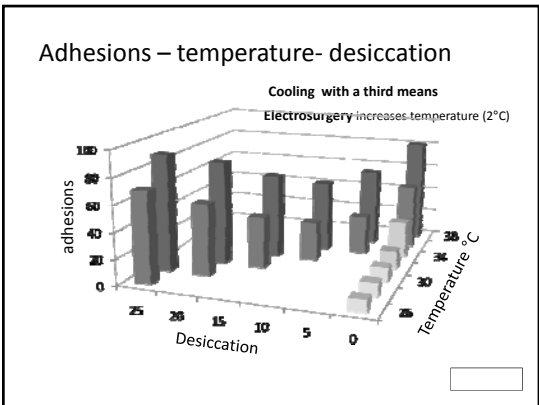


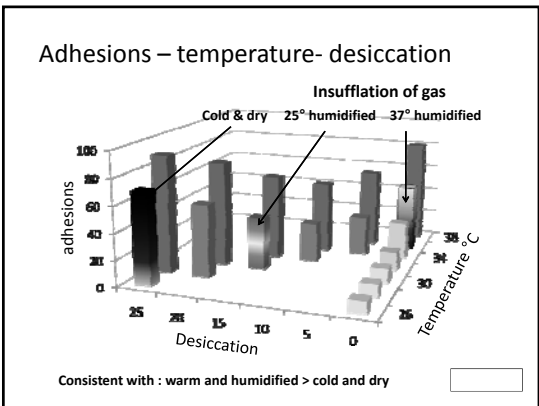
Adhesions – temperature- desiccation



Adhesions – temperature- desiccation





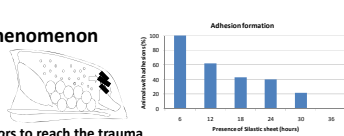


Conclusions

- Surgical Trauma is
 - necessary : no denovo adhesions
 - Quantitatively less important
- More important *20 times* is enhancement by peritoneal cavity factors
 - Bad
 - Manipulation / blood
 - Hyperoxia-hypoxia
 - dessication
 - Good
 - Cooling with a third means
 - dexamethasone
- = Acute Inflammation of superficial layers of the peritoneal cavity

Adhesion Formation & Prevention

- **Classic : a local phenomenon**
 - -> barriers
 - 40% effective
 - Local effect
 - Prevent bad factors to reach the trauma
- **New : first the peritoneal cavity -> 80% reduction**



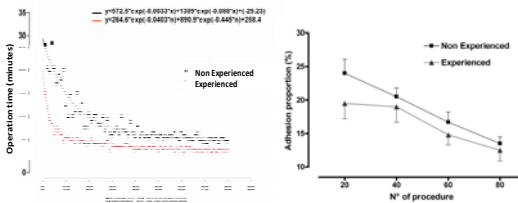
Adhesion formation

| Presence of Sterile sheet (hours) | Adhesion formation (%) |
|-----------------------------------|------------------------|
| 6 | 100 |
| 12 | 75 |
| 18 | 65 |
| 24 | 60 |
| 30 | 50 |
| 36 | 40 |

Good surgery, eg vision, time
 Peritoneal conditioning
 Dexamethasone
 Barriers

Translational research

- **1 Gentle tissue handling**



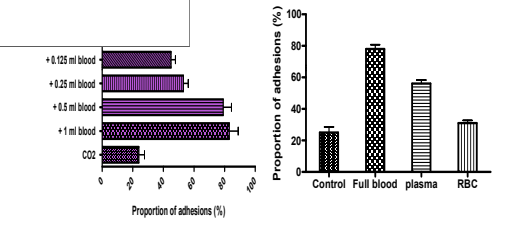
Operation time (minutes)

Adhesion proportion (%)

Corona R et al, in press Fertil Steril

Translational research

- **2 reduce blood and fibrin : use heparin in sprinkler**



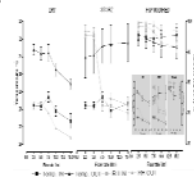
Proportion of adhesions (%)

Corona R et al, submitted

Translational research

• 3 No desiccation & reduce temperature < 32° C cooling with a third means

- If 37° 100% RH = too warm
- If 30°RH = heating in the abdomen = unavoidable desiccation
- Therefore cooling with a third means
 - Abdomen at 30°
 - Gas at 32° 100%RH
 - = condensation

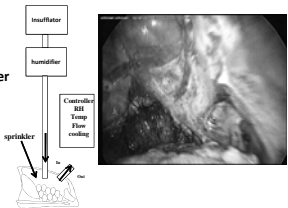


Corona R et al, in press Am J OBGYN

Translational research

• 3 No desiccation & reduce temperature < 32° C cooling with a third means

- With controller &
 - Cooling with third means
 - Esaternus modified humidifier
- At any preset temperature
- Zero desiccation

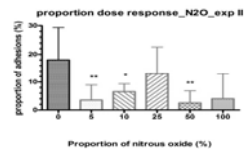


Corona R et al, in press Am J OBGYN

Translational research

• 3 Use the right gaz mixture : CO2+10% N2O+4% O2

- Single most important is N2O
 - 100% less pain
- New : 5% is enough
 - Less adhesions
 - Less pain
- Oxygen marginally effective

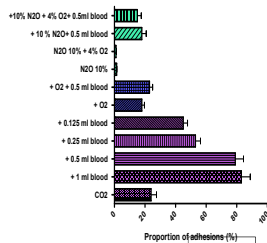


Corona R et al, submitted

Translational research

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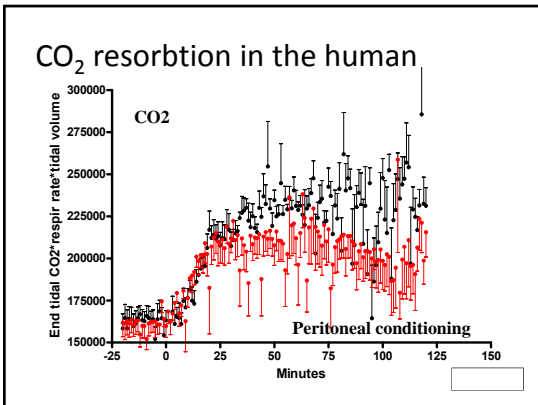
Corona R et al, submitted

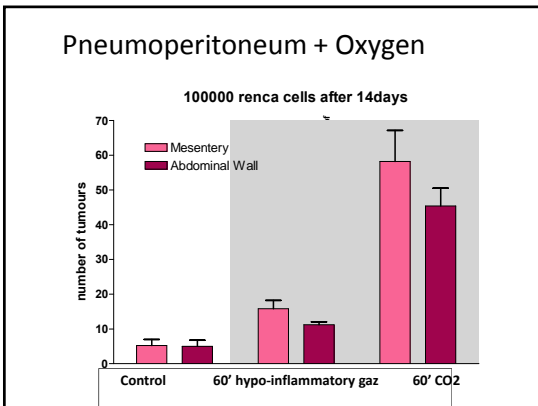
Peritoneal conditioning : human

- 4. Further reduce inflammation with Dexamethasone
- 5. Eventually load with ROS scavengers as vitamin C

Pain following promontofixtion

- RCT n=24
- CO2 versus CO2+ 4% of oxygen
- Significantly less pain day 1 and 2
- (no humidification – 5 L/min)

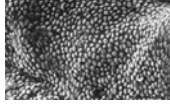




- ### Full conditioning
- Pain & pain killer intake
 - CO₂ adsorption
 - Time to first flatus and first stools
 - CRP
 - Adhesion formation

The Future : Peritoneal conditioning

- Gaz that reduces acute inflammation normoxia (3-4% of oxygen)
- Cooling with third means + Humidifier
 - No desiccation
 - <32°



- Single most effective in prevention of adhesion formation
- combination therapy & barrier > 90%

- 60% Prevention of pain
- Prevention of tumour implantation
- Decreases/abolishes CO₂ Resorbtion

I hope that shortly after finishing the RCT's
Thank you to so say : Thank you

- For less pain
and less adhesions
- less adhesions >90% - RCT with hyalobarrier as barrier
 - Less morbidity
- A. Coosemans**
R. Corona
K. Mailova
S. Mutsaers
P. Koninckx
In Laparoscopy and Laparotomy



Mark your calendar for the upcoming ESHRE campus workshops!

- Early pregnancy disorders: integrating clinical, immunological and epidemiological aspects
23-26 August 2011 - Copenhagen, Denmark
- The management of infertility – training workshop for junior doctors, paramedicals and embryologists
7-8 September 2011 - St. Petersburg, Russia
- Basic genetics for ART practitioners
9 September 2011 - Bucharest, Romania
- The whole man
22-23 September 2011 - Sevilla, Spain
- Accreditation of a Preimplantation Genetic Diagnosis Laboratory
3-4 October 2011 - Athens, Greece
- Human reproductive tissues, gametes and embryos: Innovations by science-driven culture and preservation systems
9 October 2011 - Cairns, Australia
- Comprehensive preimplantation screening: dynamics and ethics
13-14 October 2011 - Maastricht, The Netherlands
- Endometriosis and IVF
28-29 October 2011 - Rome, Italy
- Endoscopy in reproductive medicine
23-25 November 2011 - Leuven, Belgium
- What you always wanted to know about polycystic ovary syndrome
8-10 December 2011 - Sofia, Bulgaria

www.eshre.eu
(see "Calendar")

Contact us at info@eshre.eu



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