Deep Endometriosis – Diagnosis, Impact of Surgical Treatment, Future Perspectives on Therapies (Didactic)

PROGRAM CHAIR
Charles E. Miller, MD

Charles Chapron, MD
Tamer A. Seckin, MD
Camran R. Nezhat, MD
Jim Tsaltas, MD
Professional Education Information

Target Audience
Educational activities are developed to meet the needs of surgical gynecologists in practice and in training, as well as, other allied healthcare professionals in the field of gynecology.

Accreditation
AAGL is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The AAGL designates this live activity for a maximum of 3.75 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIPS
As a provider accredited by the Accreditation Council for Continuing Medical Education, AAGL must ensure balance, independence, and objectivity in all CME activities to promote improvements in health care and not proprietary interests of a commercial interest. The provider controls all decisions related to identification of CME needs, determination of educational objectives, selection and presentation of content, selection of all persons and organizations that will be in a position to control the content, selection of educational methods, and evaluation of the activity. Course chairs, planning committee members, presenters, authors, moderators, panel members, and others in a position to control the content of this activity are required to disclose relevant financial relationships with commercial interests related to the subject matter of this educational activity. Learners are able to assess the potential for commercial bias in information when complete disclosure, resolution of conflicts of interest, and acknowledgment of commercial support are provided prior to the activity. Informed learners are the final safeguards in assuring that a CME activity is independent from commercial support. We believe this mechanism contributes to the transparency and accountability of CME.
# Table of Contents

Course Description........................................................................................................................................1

Disclosure......................................................................................................................................................3

Endometriosis and Hysterectomy  
C.R. Nezhat ...................................................................................................................................................5

The Use of Robotic Assistance in the Treatment of Deep Endometriosis  
C.E. Miller ....................................................................................................................................................11

The Impact of Surgical Treatment of Endometriosis on Infertility  
J. Tsaltas .......................................................................................................................................................15

Complications  
T.A. Seckin ....................................................................................................................................................20

The Impact of Surgical Treatment of Endometriosis on Pelvic Pain  
C.E. Miller ....................................................................................................................................................24

Therapeutic Strategies for the Treatment of Extra Pelvic Endometriosis – Diaphragm, Lungs, Pleura  
C.R. Nezhat ...................................................................................................................................................33

Perspectives on the Future Treatment of Endometriosis  
C. Chapron ....................................................................................................................................................42

Cultural and Linguistics Competency ........................................................................................................56
Deep Endometriosis – Diagnosis, Impact of Surgical Treatment, Future Perspectives on Therapies (Didactic)

Charles E. Miller, Chair
Faculty: Charles Chapron, Camran R. Nezhat, Tamer A. Seckin, Jim Tsaltas

Course Description

Due to the inexperience in appreciating the diagnosis prior to surgery, the complexity of the surgery itself, and the potential need for a multidisciplinary approach, many women with deep endometriosis are not satisfactorily treated at the time of the initial laparoscopic surgery.

This course demystifies the surgical approach to deep endometriosis. This includes hysterectomy and endometriosis, robot-assisted laparoscopy for deep endometriosis, the impact of surgery for endometriosis on pain and infertility, strategies for the treatment of extra pelvic endometriosis, and a discussion on future treatments for endometriosis. Teaching will be enhanced with interactive video session, featuring all faculty members.

Learning Objectives

At the conclusion of this course, the participant will be able to: 1) Discuss strategies for laparoscopic hysterectomy in the presence of severe endometriosis; 2) describe how robotic surgery can enhance the treatment of deep endometriosis; 3) discuss the impact of surgical therapy for endometriosis on infertility and pelvic pain; 4) detect extra pelvic endometriosis and discuss surgical treatment; and 5) discuss future treatments for endometriosis.

Course Outline

1:30 Welcome, Introductions and Course Overview C.E. Miller
1:35 Endometriosis and Hysterectomy C.R. Nezhat
2:00 The Use of Robotic Assistance in the Treatment of Deep Endometriosis C.E. Miller
2:20 The Impact of Surgical Treatment of Endometriosis on Infertility J. Tsaltas
2:40 Complications T.A. Seckin
2:55 Video/Interactive Session, Q&A All Faculty
3:25 Break
3:40 The Impact of Surgical Treatment of Endometriosis on Pelvic Pain C.E. Miller
4:05 Therapeutic Strategies for the Treatment of Extra Pelvic Endometriosis – Diaphragm, Lungs, Pleura C.R. Nezhat
4:30 Perspectives on the Future Treatment of Endometriosis  C. Chapron
4:55 Video/Interactive Session, Q&A  All Faculty
5:30 Course Evaluation
PLANNER DISCLOSURE
The following members of AAGL have been involved in the educational planning of this workshop and have no conflict of interest to disclose (in alphabetical order by last name).
Art Arellano, Professional Education Manager, AAGL*
Viviane F. Connor
Consultant: Conceptus Incorporated
Frank D. Loffer, Executive Vice President/Medical Director, AAGL*
Linda Michels, Executive Director, AAGL*
Jonathan Solnik
Other: Lecturer - Olympus, Lecturer - Karl Storz Endoscopy-America

SCIENTIFIC PROGRAM COMMITTEE
Arnold P. Advincula
Consultant: CooperSurgical, Ethicon Women's Health & Urology, Intuitve Surgical
Other: Royalties - CooperSurgical
Linda Bradley
Grants/Research Support: Elsevier
Consultant: Bayer Healthcare Corp., Conceptus Incorporated, Ferring Pharmaceuticals
Speaker's Bureau: Bayer Healthcare Corp., Conceptus Incorporated, Ferring Pharm
Keith Isaacson
Consultant: Karl Storz Endoscopy
Rosanne M. Kho
Other: Honorarium - Ethicon Endo-Surgery
C.Y. Liu*
Javier Magrina*
Ceana H. Nezhat
Consultant: Intuitve Surgical, Lumenis, Karl Storz Endoscopy-America
Speaker's Bureau: Conceptus Incorporated, Ethicon Women's Health & Urology
William H. Parker
Grants/Research Support: Ethicon Women's Health & Urology
Consultant: Ethicon Women's Health & Urology
Craig J. Sobolewski
Consultant: Covidien, CareFusion, TransEnterix
Stock Shareholder: TransEnterix
Speaker's Bureau: Covidien, Abbott Laboratories
Other: Proctor - Intuitve Surgical

FACULTY DISCLOSURE
The following have agreed to provide verbal disclosure of their relationships prior to their presentations. They have also agreed to support their presentations and clinical recommendations with the “best available evidence” from medical literature (in alphabetical order by last name).
Charles E. Miller
Grants/Research Support: Covidien, Femasys, Olympus, Novartis, Abbott Laboratories
Consultant: Covidien, Femasys, Abbott Laboratories, Ferring Pharm
Charles Chapron*
Camran R. Nezhat*
Tamer A. Seckin*
Jim Tsaltas  
Grants/Research Support: Covidien, Merck Serono  
Scott G. Chudnoff*  

Asterisk (*) denotes no financial relationships to disclose.
Disclosure

- I have no financial relationships to disclose.

Objectives

- Describe techniques for safe laparoscopic access
- Describe techniques used in difficult hysterectomies
- Describe techniques used to address difficult adhesions during laparoscopy

Communicate with your Anesthesiologist

- Describe your anticipated procedure
- Estimated blood loss
- Estimated duration
- Preoperative antibiotics

How can we reduce risk of complication?

- Review normal anatomy
- How to develop retroperitoneal dissection
- Discuss preoperative planning
- Examine proper instrumentation and techniques for dissection
- Review possible complications and management
Step 1 – Know the Anatomy

- Abdominal wall
- Ligaments
- Avascular spaces
  - Para-vesical space
  - Vesico-vaginal space
  - Vesico-uterine space
  - Recto-vaginal space
- Vascular structures
Intraperitoneal view of the sacral promontory and the location of the bifurcation of Aorta (*)

Middle sacral vessels are in the midline on the sacrum.

The relationship of bladder, ureters and rectum after a radical hysterectomy

Step 2 - Patient Positioning

- The patient is in supine position
- The thighs are not flexed so that the suprapubic and lateral trocars may be maneuvered
- Nasogastric tube is placed before procedure
The buttocks are hanging 2-3 inches off the table.

Ensure the patient is completely relaxed.

Step 3 – Palpation of aorta

The aorta and sacral promontory are palpated.
Step 4 – Insertion of Veress needle

Veress needle is grasped by the shaft and directed posteriorly at a 90° angle. Inset shows elevation of skin and subcutaneous tissue by towel clips.

Operative Gynecologic Laparoscopy: Principles and techniques

Accessory Trocars

- Standard laparoscopy
  - Two to three 5 mm ports
  - 2 lateral
  - 1 supra-pubic
- Robotic
  - Three to four 5-8 mm ports
  - Similar configuration
  - Configuration may be altered depending on surgery

Before positioning the robotic cart, pressure points must be carefully padded

In the case of an airway emergency or cardiac arrest, resuscitating the patient requires disengaging the robotic instruments before backing the cart away from the OR table

Avoid head docking and use side or between legs docking when possible.
Thank You!

Fellows

Jackie Miller, DO
Elizabeth Buescher MD
M. Ali Parsa, MD
Chandhu Paka, MD
The Use of Robotic Assistance in the Treatment of Deep Endometriosis

Charles E. Miller, MD, FACOG

- President, International Society for Gynecologic Endoscopy (ISGE)
- President, AAGL (2007-2008)
- Clinical Associate Professor, Department OB/GYN, University of Illinois at Chicago, Chicago, IL USA
- Director of Minimally Invasive Gynecologic Surgery, Advocate Lutheran General Hospital, Park Ridge, IL USA
- Director, AAGL/SRS Fellowship in Minimally Invasive Gynecologic Surgery, Advocate Lutheran General Hospital, Park Ridge, IL USA

Disclosure

- Grants/Research Support: Covidien, Femasys, Olympus, Novartis, Abbott Laboratories
- Consultant: Covidien, Femasys, Abbott Laboratories, Ferring Pharm

The Use of Robotic Assistance in the Treatment of Deep Endometriosis

Objectives

1. List two advantages of robotic assisted surgery.
2. List two areas where robotics positively assists minimally invasive gynecologic surgery.
3. Discuss the impact of robotic surgery on the treatment of superficial and deep endometriosis.

Robotic surgery has proven to be a viable alternative for multiple procedures in minimally invasive gynecologic surgery.

Advantages of robotic assistance in minimally invasive gynecologic surgery

- Eliminates tremor (filters movement)
- Scales down hand movement (more precise)
- Stereoscopic viewer at console
- Enables 3D imaging
- Steady image
- Advanced ergonomics – instrument articulation provides seven degrees of movement (mimics human wrist movement and eliminates fulcrum effect)
- Reduces physician fatigue

Disadvantages of Robotic Assistance in Minimally Invasive Gynecologic Surgery

- Cost
  - Robot $1.5 - $1.75 million
  - Reusable instruments (10 time use) - $250 (average cost per use)
- Lack of tactile feedback (visual haptics)
- Need for well qualified assistant
- Learning curve (albeit short)
- Potential loss of laparoscopic (suturing) skills
The Use of Robotic Assistance in the Treatment of Deep Endometriosis

Robotic Assisted Laparoscopic Hysterectomy

A Comparison of Total Laparoscopic Hysterectomy to Roboticically Assisted Hysterectomy: Vaginal Outcomes in a Community Practice

Thomas N. Payne, MD, and Emily K. Steinwachs

Postoperative Outcomes of Robotic Assisted Hysterectomy for Benign Cases With Complex Pathology

Harris B. Lowe, MD

Robotic Assisted Laparoscopic Hysterectomy vs Traditional Laparoscopic Hysterectomy: Five Metanations

Michelle Scambler, Leslee Garzara, Marco Vrachnak, and Rashi Pandey

Boggess JF, Obstet Gynecol 2009; 114: 585-593

Robotic Assisted Radical Hysterectomy for Cervical Cancer

The Use of Robotic Assistance in the Treatment of Deep Endometriosis

Lowe MP, Gynecol Oncol 2009; 113:191-4
Cantrell LA, Gynecol Oncol 2010; 117: 260-5

Robotic Assisted Hysterectomy for Endometrial Cancer

Mok ZW, Int J Gynecol Cancer 2012; 22(5): 819-25
Leitao MM, Gynecol Oncol 2012; 125(2): 394-9. Epub 2012 Feb 1
Lim PC, JMIG 2010; 17(6): 739-48
Gehrig PA, Gynecol Oncol 2008; 111: 41-5

Robotic Assisted Hysterectomy Sacrocolpopexy


Robotic Assisted Myomectomy

Barakat E, Obstet Gynecol 2011; 117: 256-65

The Last Frontier

Robot Assisted Endometriosis Surgery for Deep Infiltrative Surgery

Currently, literature is comprised of only feasibility studies, no large case series and certainly no randomized controlled reports.
Robotic assisted endometriosis surgery for deep infiltrative disease

The use of robotic assistance in the treatment of deep endometriosis

- N=1 N=7 stage III, 2 stage IV

- Nezhat C, Fertil Steril 2010; 94(7):2758-60
- Frick AC, JSLS 2011; 15:396-99
- Brudie LA, J Robotic Surgery, published on-line October 2011

- N=2
- N=80 stage IV (2 parametrium, 6 rectovaginal septum, 10 sigmoid serosa, 4 cecum)

- N=2
- N=26 stage IV

Robotic assisted endometriosis surgery for deep infiltrative disease

- 22 consecutive robot assisted complete laparoscopic excisions of deep infiltrative endometriosis with colorectal involvement 3/10 to 5/11
  - Segmental resection
    - N=12
    - Median nodule 35mm
  - Shaving
    - N=10
    - Median nodule 30mm
  - Surgical technique
    - Umbilical access vs. right periumbilical (bowel resection)
  - Instrumentation
    - Monopolar scissors
    - Monopolar hook
    - Bipolar forceps
    - Large needle holder

Surgical and anatomicopathologic findings

Post operative findings

Six month follow up

Pre and post operative symptoms on VAS analogue scale (19 patients)

- Median operative time and hospitalization comparable to historical conventional laparoscopy data 1,2,3
- Median blood loss and blood transfusion rate improved over historical conventional laparoscopy data 1,2
- Rectovaginal fistula in 13 patients undergoing vaginal resection (major risk at conventional laparoscopy) 1,4

Despite the recognized advantage of increased precision in robotic assisted surgery, deep infiltrative endometriosis creates increased challenges for the robotic surgeon.

Grasping
# The Use of Robotic Assistance in the Treatment of Deep Endometriosis

Robotic Assisted Endometriosis Surgery for Deep Infiltrative Disease

<table>
<thead>
<tr>
<th>Instrument Name</th>
<th>Cannula Size</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>400189 420189 8MM DOUBLE FEN Estrated GRASPER</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>400208 420208 8MM THORACIC GRASPER</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>400177 420177 5MM BOWEL GRASPER</td>
<td>3.50 Very Low</td>
<td></td>
</tr>
<tr>
<td>400278 420278 8MM GRASPING RETRACTOR</td>
<td>4.00</td>
<td></td>
</tr>
<tr>
<td>400139 420139 5MM SCHERTEL GRASPER</td>
<td>5.00</td>
<td></td>
</tr>
<tr>
<td>400143 420143 5MM MARYLAND DISSECTOR</td>
<td>5.00</td>
<td></td>
</tr>
<tr>
<td>400176 420176 5MM BULLET NOSE DISSECTOR</td>
<td>5.00</td>
<td></td>
</tr>
<tr>
<td>400207 420207 8MM TENACULUM FORCEPS</td>
<td>6.00</td>
<td></td>
</tr>
<tr>
<td>400145 420145 5MM DEBAKEY FORCEPS</td>
<td>6.00</td>
<td></td>
</tr>
<tr>
<td>400203 420203 8MM PERICARDIAL DISSECTOR</td>
<td>6.00</td>
<td></td>
</tr>
<tr>
<td>400173 420173 5MM HARMONIC CURVED SHEARS</td>
<td>6.50 Low</td>
<td></td>
</tr>
<tr>
<td>400174 420174 8MM HARMONIC CURVED SHEARS</td>
<td>6.50</td>
<td></td>
</tr>
<tr>
<td>400227 420227 8MM PK DISSECTING FORCEPS</td>
<td>6.50</td>
<td></td>
</tr>
<tr>
<td>400048 420048 8MM LONG TIP FORCEPS</td>
<td>6.50</td>
<td></td>
</tr>
<tr>
<td>400049 420049 8MM CADIERE FORCEPS</td>
<td>7.00</td>
<td></td>
</tr>
<tr>
<td>400190 420190 8MM COBRA GRASPER</td>
<td>7.00</td>
<td></td>
</tr>
<tr>
<td>400146 420146 5MM CURVED SCISSORS</td>
<td>7.50</td>
<td></td>
</tr>
<tr>
<td>400121 420121 8MM FINE TISSUE FORCEPS</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>400205 420205 8MM FENESTRATED BIPOLAR FORCEPS</td>
<td>8.50</td>
<td></td>
</tr>
<tr>
<td>400141 420141 5MM ROUND TIP SCISSORS</td>
<td>9.00</td>
<td></td>
</tr>
<tr>
<td>400110 420110 8MM PRECISE BIPOLAR FORCEPS</td>
<td>9.00</td>
<td></td>
</tr>
<tr>
<td>400172 420172 8MM MARYLAND BIPOLAR FORCEPS</td>
<td>9.00</td>
<td></td>
</tr>
<tr>
<td>400171 420171 8MM MICRO BIPOLAR FORCEPS</td>
<td>9.50 Medium</td>
<td></td>
</tr>
<tr>
<td>400033 420033 8MM BLACK DIAMOND MICRO FORCEPS</td>
<td>9.50 Medium</td>
<td></td>
</tr>
<tr>
<td>400117 420117 5MM NEEDLE DRIVER</td>
<td>9.50</td>
<td></td>
</tr>
<tr>
<td>400178 420178 8MM CURVED SCISSORS</td>
<td>10.00</td>
<td></td>
</tr>
<tr>
<td>400181 420181 8MM RESANO FORCEPS</td>
<td>10.00</td>
<td></td>
</tr>
<tr>
<td>400036 420036 8MM DEBAKEY FORCEPS</td>
<td>11.50</td>
<td></td>
</tr>
<tr>
<td>400179 420179 8MM MONOPOLAR CURVED SCISSORS</td>
<td>12.00</td>
<td></td>
</tr>
<tr>
<td>400093 420093 8MM PROGRASP FORCEPS</td>
<td>12.00 High</td>
<td></td>
</tr>
<tr>
<td>400001 420001 8MM POTTS SCISSORS</td>
<td>12.50</td>
<td></td>
</tr>
<tr>
<td>400007 420007 8MM ROUND TIP SCISSORS</td>
<td>12.50</td>
<td></td>
</tr>
<tr>
<td>400006 420006 8MM LARGE NEEDLE DRIVER</td>
<td>16.00</td>
<td></td>
</tr>
<tr>
<td>400209 420209 8MM SUTURECUT NEEDLE DRIVER</td>
<td>17.00 Very High</td>
<td></td>
</tr>
<tr>
<td>400194 420194 8MM MEGA NEEDLE DRIVER</td>
<td>19.00</td>
<td></td>
</tr>
</tbody>
</table>

## References

- Boggess JF, Obstet Gynecol 2009; 114: 585-93
- Lowe MP, Gynecol Oncol 2009; 113: 191-4
- Cantrell LA, Gynecol Oncol 2010; 117: 260-5
- Gehrig PA, Gynecol Oncol 2008; 111: 41-5
- Aschim T, 2002; 119: 129-135
- Fanifani F, Fertil Steril 2010; 94: 444-49
What evidence supports surgical interventions in the management of endometriosis-related infertility

AAGL - 2012

Dr Jim Tsaltas
President AGES
Head Of Gynaecological Endoscopy
Southern Health & Monash Medical Centre
Monash University
Senior Infertility Specialist Melbourne IVF

Introduction

Scope of my talk
What evidence supports surgical intervention in the management of endometriosis-related infertility

Topics considered in preparation

- Minimal to Mild Endometriosis
- Endometriomas
- DIE (deep infiltrating endometriosis)
- Inclusion of rectovaginal and colorectal endometriosis
- Surgical technique
- Adhesion prevention
- Pre and post surgical adjunct medical therapy
- Repeat surgery
- Place of surgery for failed IVF
- No surgery at all

In preparation of this talk

- I have taken the starting point that the patient has been diagnosed with endometriosis and they are infertile
- Diagnosis modality can include examination, ultrasound, laparoscopy
- The infertile population we review are couples with no significant male factor infertility, the female partner is ovulatory and has patent tubes
- Intervene at 12 mths of infertility if under age of 35 or at 6 months if 35 or over

The use of laparoscopic surgery in the treatment of subfertility related to minimal and mild endometriosis may improve future fertility

Consensus: On weight and high grade of evidence laparoscopic surgery is recommended for minimal – mild endometriosis to enhance fertility

Importance of ongoing laparoscopic skills training
- Surgery must remain an option – Barri etal 2010

Minimal to Mild: surgical treatment for subfertility

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Number</th>
<th>Year</th>
<th>Patient pop</th>
<th>surgery</th>
<th>Control</th>
<th>Outcome</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcoux</td>
<td>NEJM</td>
<td>1997</td>
<td>337</td>
<td>20-39yo, infertile &gt;12m</td>
<td>resection/ablation or control</td>
<td>pregnancy</td>
<td>29/169 (17.7%)</td>
<td>50/172 (30.7%)</td>
</tr>
<tr>
<td>Gruppo italiano</td>
<td>Human Reproduction</td>
<td>1999</td>
<td>14</td>
<td>&lt;36yo, Infertile &gt;2 years</td>
<td>resection/ablation or control</td>
<td>pregnancy</td>
<td>13/47 (28.9%)</td>
<td>12/54 (23.5%)</td>
</tr>
</tbody>
</table>

Disclosures

- Grants/Research Support: Covidien, Merck Serono

Minimal – Mild Endometriosis

- The use of laparoscopic surgery in the treatment of subfertility related to minimal and mild endometriosis may improve future fertility
- Surgery involving ablation/excision (+/- adhesiolysis) is effective compared to diagnostic laparoscopy
- Evidence is high quality
  - 2 RCTs (Marcoux et al 1997, Gruppo Italiano 1999)
  - Meta analysis of the two
  - Meta analysis plus previous effect whereas Gruppo Italiano reported a small negative effect
  - Jacobsson et al. – Cochrane review 2012
  - Limitations of studies discussed by Cochrane and Vercellini etal (2009)
- Consensus: On weight and high grade of evidence laparoscopic surgery is recommended for minimal – mild endometriosis to enhance fertility
- Importance of ongoing laparoscopic skills training
- Surgery must remain an option – Barri etal 2010
Moderate to severe endometriosis
- Will break down into endometriomas (ovarian disease) and also rectovaginal /DIE (including colorectal endometriosis)
- Must remember they are not separate entities and may co-exist and according to the literature endometriomas are often markers of more severe disease (Banerjee 2008, Chapron 2009)
- For this discussion I will separate the discussion into:
  - management of Ovarian disease (endometriomas)
  - management of rectovaginal endometriosis /DIE (including colorectal disease)
- Need to consider place of surgery, associated symptoms such as pain, access and costs of both surgery and IVF.
- Laparoscopic skill acquisition and training are vital.

Ovarian endometriomas
- Many studies have been produced to discuss this topic:
  - Guidelines to date – ESHRE (2008), ASRM (2006), NHS (2010) – There may be a possible benefit
  - What is the Dely?
  - Laparoscopic cystectomy by excisional surgery for endometriomata 4cm or greater improves fertility/pregnancy marker rates) compared to drainage and coagulation (Beretta 1998, Alborzi 2004).
  - Many other observational studies show an increased pregnancy rate after surgery for endometriomas with a weighted mean of 50% – summarized in Vercellini 2009 and listed in bibliography of this talk
  - As well as improved fertility rates excision has lower recurrence of endometriomas and symptoms (Ban 2000 and updated 2011 – cochrane review).
  - High quality evidence RCT – limitation not including expectant arm in trial – may influence evidence to moderate quality as we do not know true rate of pregnancy with no surgery

Decisions to treat
- Based on the above evidence
- Weight of other studies
- Other symptoms attributed to the endometriosis – significant pain, impact on patients QOL, histological diagnosis, reduce risk of cyst complications, improve access for IVF if required and reduce risk of post IVF abscess formation (Garcia-Velasco 2009)
- Tubal and Male factor infertility
- Access to trained surgeons and IVF
- Must no look at surgery and IVF as competing interests but rather as complementary therapeutic strategies (Barri 2010, Littman 2005, Adamson 2005)

Issues related to treatment
- Early studies suggested minimal if any damage to the ovarian reserve after surgical treatment for endometriomas – (Loh 1999, Donnez 2001, Canis 2001)
- Recent studies however have demonstrated damage to the ovarian reserve
- Methodology to assess this includes D2 FSH, AFC, Ovarian reserve, response to gonadotrophs in IVF and AMH
- Damage may also relate to size of endometrioma being excised (Roman 2010)

Reducing Risks
- Care with surgical technique
  - Excision is preferred method
  - Care with identification of planes
  - Minimize diathermy and conserve all ovarian tissue possible
  - Recent small randomized clinical trial – shows potential less reduction in ovarian reserve when suturing is used for haemostasis - AFC outcome measure (Coric 2011)
  - Combined technique – excisional surgery and also ablative surgery for 10 – 20% of endometrioma wall next to hilus (Donnez 2010)
  - AMH excellent marker
  - Group should consider recommendation of routine AMH testing pre and 3 months post endometriosis surgery
  - Group should consider egg freezing prior to recurrent endometrioma surgery in young patient with low AMH not trying to conceive
Ovarian Endometriomas

Consensus statement proposal

- Evidence of moderate to high grade exists to recommend excisional surgery for endometriomas 4cm or more to improve fertility. Appropriate skill and training is required for safe and complete excision. It is important to minimize ovarian damage and further studies are required to ascertain if suturing for haemostasis is superior. Surgeons should consider measurements of ovarian reserve pre and post operative to help counsel patients.

Adhesions

- Small study looked at reduction of post operative adhesions by suture to close the ovary for haemostasis compared to traditional diathermy (endometriomas) RCT – favored suturing – Pellicano 2008
- This is now our practice
- 2 Cochrane reviews
  - Ahmed 2010 – Barrier agents for adhesion prevention after gynaecological surgery
  - Do reduce post operative adhesions
  - No data regarding pregnancy outcome

Adhesions (cont)

- Methally 2011 – Fluid and pharmacological agents for adhesion prevention after gynaecological surgery
- There is no evidence of a benefit of using the above agents as an adjunct during pelvic surgery for improving pregnancy outcomes
- Consensus:
  - No data to support the routine use of adhesion barriers to improve pregnancy outcomes

Surgery for Rectovaginal Lesions

- Early studies suggested improvement in fertility rates after management of DIE (Chapron 1999)
- Since that time a number of articles have been published discussing this issue
  - Severe endometriosis which infiltrates the posterior vaginal wall and anterior rectal wall is one of the most challenging surgical issues we face as gynaecologists.
  - There have been a number of studies on this topic. Studies are either retrospective, observational or prospective.
  - Surgery may be challenging and the risks of intraoperative and post operative morbidity not negligible.
  - Surgery should only be performed with the appropriate multidisciplinary set up.
- Pregnancy rates from studies quoted vary from 23 - 57% (recent review Meuleman 2011) These studies vary in quality and the grade of evidence are mostly low quality with occasional moderate quality studies

Recent Studies of interest

- Ferrero 2009 Pregnancy after bowel resection
  - Surgery
    - Laparoscopy – 57.6%, Laparotomy – 23.6%
  - Surgical technique based on the preference of the colorectal surgeon
  - Laparoscopic superior to laparotomy
  - No Spont Preg in women over 35 after surgery
  - Pregnancy rates from studies quoted vary from 23 - 57% (recent review Meuleman 2011)

Studies Continued

- Vercellini 2006
  - 105 women – 44 chose surgery, 61 expectant management
  - Patients self selected
  - Surgery by laparotomy for severe rectovaginal endometriosis
  - 24 month follow up
  - Surgery = 44.9%
  - Expectant management = 65.8%
  - Bias as stated by authors – patients with more pain and potentially more aggressive disease chose surgery and this may influence pregnancy rates
Studies Continued

- Barri 2010
  - Observational study
  - 825 patients aged 20 – 40 years (mean age 35.3) with infertility and endometriosis – 2001 to 2008
  - Mean length of infertility – 3.2 ± 2.3 years
  - Diagnosed – stage 3 – 4 AFS Endometriosis
  - Many with endometriomas
  - 483 patients – surgery – 262 spont pregnancies 58.5%
  - 221 patients – no pregnancy – 144 IVF – 184 Oocyte retrieval and 56 pregnancies
  - IVF chosen by 173 patients who chose no surgery – 68 pregnancies (patients matched)
  - Age is an issue in both groups (35 yoa)
  - Surgery only – <35 – 229/372, >35 – 33/111
  - Group 3 – no treatment – 20/69 – 11.8%
  - Good study – favoring surgery
  - If under 35 – Ivf at 12 months, if over 35 – Ivf at 6 months

Deep Infiltrating Endometriosis and IVF

<table>
<thead>
<tr>
<th></th>
<th>IVF only (n=105)</th>
<th>Surgery + IVF (n=46)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility duration (mo)</td>
<td>29 ± 20</td>
<td>35 ± 18</td>
<td>.01</td>
</tr>
<tr>
<td>Total dose of FSH (IU)</td>
<td>2380 ± 911</td>
<td>2542 ± 1012</td>
<td>.01</td>
</tr>
<tr>
<td>Number of oocytes retrieved</td>
<td>10 ± 5</td>
<td>9 ± 5</td>
<td>.04</td>
</tr>
<tr>
<td>Fertilisation rate (%)</td>
<td>77.9</td>
<td>77.1</td>
<td>.76</td>
</tr>
<tr>
<td>No. of top quality embryos/patient</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td>.1</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td>.1</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>19 ± 25.1</td>
<td>34.1 ± 30.6</td>
<td>.03</td>
</tr>
<tr>
<td>Pregnancy rate (%)</td>
<td>24</td>
<td>47</td>
<td>.04</td>
</tr>
</tbody>
</table>

(Bianchi et al J Min Invas Gyn 2009)

Surgical Technique

- Debate between the need for bowel resection vs shaving technique only for deep rectovaginal endometriosis
- Donnez 2010
  - Prospective analysis of 500 cases
  - 388 patients wished to conceive – 221(57%) spontaneous pregnancies
  - 167 – needed IVF – failure to conceive after 12 months of trying or immed IVF due to male factor (25% of this group)
  - 107 conceived
  - Overall pregnancy rate of 84%

Our Data

Tsaltas J, Cooper M, Reid G

- Total Group – 257 patients - colorectal endo (to 30/8/2010
- 75 Infertility
  - 19/75 – 25.3% infertility, 56/75 – 74.7% pain and infertility
  - 43 segmental resection, 28 disc excision, 4 multiple procedures
  - 7 lost to follow up, 11 no longer wished to conceive
  - 57 available to follow up still wishing to conceive
  - Pregnancy rate – 73.6 %
  - 25.9% - spont, 68.5% ART (IVF), 5.6% mode of preg not recorded

Decision to treat

- When and how to treat each patient has become much more individualized
- Full discussion about options
- Place of IVF and/or surgery
- Consider patients age, male factor, ovarian reserve, ability to access the ovary safely for OPU, endometriosis pain symptoms and impact on QOL
- Pre-Operative Ultrasound to assess the size and level of invasion of the rectal lesion
- Consent can be appropriately obtained
- Plan mode of probable surgery – shave, disc, excise
- Fold up – LDR and IVF immed or set time for spont conception pre IVF

Severe endometriosis including colorectal disease: Consensus

- Infertile patients with severe endometriosis including colorectal disease should consider surgery as an alternative to IVF. There are no RCT or meta-analyses to answer the question whether the surgical excision of severe endometriosis will enhance pregnancy rates. However recent studies of better quality and larger numbers suggest an improvement in pregnancy rates. Surgery should only be undertaken with appropriate consent and understanding of the risks. Women should be given a full understanding of all available options to help with conception. Surgery for this major disease should be managed by the appropriate multidisciplinary team.
Medical Therapy before or after surgery
- Cochrane review
- Furness 2004
  - Pre and post-operative medical therapy for endometriosis surgery
  - No evidence of benefit to surgery alone
- Consensus – no benefit of medical therapy before or after endometriosis surgery for infertility

Repeat Surgery
- Limited information available on the effect of second line surgery for recurrent endometriosis in fertile women.
- No studies have compared repeat surgery vs expectant management; IVF vs repeat surgery.
- Studies:
  - Furness 2004 – 1961 to 2002
    - 129 primary surgeries and 75 reoperations for recurrent endometriomas in 30 women, all over the age of 18.
    - Patients had recent primary surgery and were reassessed post-operatively for recurrent endometriomas.
  - The surgical procedure might be technically more challenging and involves a greater risk of further impairment of function.
  - 37.5% of the women had a pregnancy after repeat surgery, compared to 25.8% after primary surgery.
- Analysis of the literature – achieving a pregnancy after repetitive surgery was almost half that observed after primary surgery.
- 2 cycles of IVF better than repeat surgery.
- Adamson 2005
  - Disadvantages of surgery – potential damage to ovarian reserve, morbidity, a potential longer time to conception compared to IVF, and lack of trained surgeons.
- ESHRE 2005
  - Final decision should consider presence of pain symptoms and large endometriomas. Pain and refusal to proceed to IVF still constitute an indication for repeat surgery.
- No evidence to recommend repeat surgery over IVF.

Consensus on repeat surgery
- No evidence to recommend repeat surgery over IVF.
- However should consider surgery if increasing pain, enlarging endometrioma and no desire for IVF. Surgery can be complex and appropriate consent needs to be obtained.
- Grade of Evidence is Low
- More studies required

Failed IVF no previous surgery
- Littman 2005
  - Study in a tertiary IVF and Endoscopy centre
  - Retrospective case series
  - 29 patients with prior IVF failures – 22 conceived after laparoscopic treatment of endometriosis.
  - 15 spontaneous conceptions
  - 7 IVF pregnancies
  - Authors believe that complete and thorough microsurgical eradication of endometriosis allows patients to conceive without further IVF therapy and may help optimize success for those who require subsequent IVF cycles.
- Prospective cohort study – Bianchi 2009 – Previously discussed

Consensus – surgery post IVF
- Surgery may play a role in patients who have failed IVF treatment and endometriosis. It may be inappropriate to continue with repeated IVF cycles without considering surgery to excise the endometriosis. Excision of endometriosis may enhance opportunity to conceive spontaneously and even enhance IVF outcomes.
- Level of evidence - low

Conclusion
- We have a responsibility to know the evidence and be able to present it to our patients in a measured and informed manner.
- Surgery and IVF should not be seen as competing interests but as an integral part of the treatment equation.
- The appropriate multidisciplinary team needs to be available to manage many of these complex issues and patients.
- Must consider the ovarian reserve and its preservation following our intervention.
Preventing Complications of Deep Endometriosis Surgery: 
Traps, Tips & Tricks

Tamer A. Seckin, MD, FACOG, ACGE
Director, Park East Gynecology & Surgery
Founder & President, Endometriosis Foundation of America
Preceptor, AAGL Minimally Invasive Gynecologic Surgery Fellowship
North Shore LIJ–Lenox Hill Hospital
New York City, New York

Endometriosis is a debilitating, costly disease fraught with diagnostic delay, high treatment failure and recurrence. True surgical resection and treatment poses formidable challenges even the hands of experienced clinicians. In an effort to assist surgeons to provide optimal surgical intervention for women with endometriosis, this segment will review recognition and impact of procedural complications and identify appropriate strategies to reduce morbidity and thus optimize patient outcome.

At the conclusion of this segment, the participant will be able to:
1) discuss common complications of surgery for deep disease; and
2) describe techniques for reduction, management and prevention.

If we are to achieve significant progress for women with endometriosis, we must emphasize the single most important step of action:

Improve the quality of surgery.

~Tamer Seckin, MD, FACOG

Deep Endometriosis
- Deep endometriosis together with cystic ovarian endometriosis represents most severe form of disease
- Defined as endometriosis infiltrating deeper than 5-6 mm under the peritoneum
- Excision remains treatment of choice for subsequent fertility and pelvic pain;
- Difficult to treat due to proximity of and common infiltration in and around bowel, ureter, uterine artery
- Surgery for deep endometriosis may be “more difficult than surgery for cancer”
Q: Which surgical procedure is 100% safe?  
A: The one that is not performed.¹

- Laparoscopy largely safe and effective  
- Gold standard for endometriosis treatment  
- Associated with decreased morbidity and admission periods²  
- However, traumatic complications may still occur³ (e.g. bowel, bladder or gastric perforation; large vessel or ureteral injury)

### Potential Complications of Deep Endometriosis Surgery

- Postoperative urinary retention⁴  
- Rectovaginal fistula⁵  
- Ureterovaginal fistula⁶  
- Ureteric damage requiring radiological stenting⁷  
- Ureter injury⁸  
- Colonic/Bowel⁹  
- Nerve injury⁰  
- Anastomotic Leak  
- Rectovesical Fistula  
- Ureterorectal Fistula

### Incidence

- May relate to surgeon experience & severity of pathology present¹  
- Certain complications are unpreventable²; others may not be true complications³ (e.g. unintentional entry to bowel in cases of severely fibrotic, rectovaginal disease should not be viewed as complication but rather, a necessity for effective treatment)

- Inferior epigastric vessels most common complications, followed by bowel/intestinal⁴  
- Bladder injury rates comparable (0.02%-8.3%); most common with LAVH⁵

### Despite These Potential Risks...

- Laparoscopic complete excision of endometriosis offers long-term relief in most patients and should be considered the “Gold Standard.”¹  
- Minimally invasive access is generally well tolerated with reasonable incidence of complication and low recurrence rate.²
Video/Photo of complication(s)

INSERT HERE

Precautionary Pearls

• Multidisciplinary approach is imperative
• Expertise and skill of surgeon should be weighted against difficulty of excision and complexity of disease
• Meticulous post-operative care
• Expect complications and be prepared to promptly address them
• Do not be trapped into delaying effective surgical intervention, i.e. discoid resection, as primary treatment for well-selected patients with deeply infiltrating endometriosis and related debilitating symptoms

Tips & Tricks for Risk Reduction & Management

• Videoregistration & Consent
• Appropriate operator training
• Scrupulous adherence to proper technique
• Adequate pre-operative preparations
  e.g. imaging, bowel prep, medical pretreatment, etc.

Videoregistration

• “Videorecording of procedure is expected to increase quality while decreasing costs” - Koninckx
• Increases alertness, slows speed of intervention, leads to improved timely diagnosis and intervention in complications
• Medicolegal support of surgeon performance

Operator Training

• “When in doubt, refer the patient out”
• Complications diminish with increasing experience
• Planning for complete surgical excision...should be “ensured by a team of experts familiar with endometriosis, its multiple manifestations, and its management.”-Mereu, et al.

Scrupulous Adherence to Proper Technique: Ureter

• Ureteral injury can be caused by ligation, ischemia, resection, transaction, crushing, or angulation; particularly troublesome sites includes infundibulopelvic ligament, ovarian fossa and ureteral tunnel (Nezhat)
• Knowledge of pelvic path key to prevention
• Retroperitoneal laparoscopic isolation and inspection of both ureters helps diagnose ureteral involvement, which may be silent
• Appropriate use of preoperative IVP and MRI with contrast in select patients may diagnose obstruction and allow surgical planning
• Preoperative cystoscopy and ureteral stent application
• Protect ureter using hydrodistention and resecting affected peritoneum
• Intraoperative repairs include partial resection and anastomosis, suturing, stenting
• Do not hesitate to consult urologist (Nezhat et. al.)
Scrupulous Adherence to Proper Technique: Bowel

- Adequate preoperative preparations (e.g., bowel prep (throughly debated), medical pretreatment can facilitate minimal access, reduce risk of infection and permit successful management of complications)
- Transrectal MRI and transrectal ultrasonography may be useful in preoperative evaluating depth of disease infiltration
- Avoid Blunt Dissection, as this may result in small bowel obstruction
- Copious lavage, antibiotic coverage are essential in small colonic wounds
- Meticulous anatomic recognition and isolation
- Team-oriented approach reduces operator fatigue and potential for impaired judgment
- Careful suturing techniques intraoperatively can repair colonic lacerations
- Resecting part of bowel wall followed by endoscopic suturing may be uneventful, suggesting that opening of rectum during resection of deep endometriosis should not be considered a true complication

Scrupulous Adherence to Proper Technique: Bladder

- Risks include perforation, laceration, thermal damage; bladder injuries are 2 to 3 times more common than ureteral injuries
- Care must be taken not to damage intramural part of ureter during removal of deep disease
- Ensure complete pre-operative drainage of bladder
- Continuous monitoring of gaseous distention of urinary bag can aid in early detection of bladder perforation
- Laser ablation, adhesiolysis in anterior Douglas Pouch may predispose to injury if backstop or hydrodistention not used
- Injuries of >5mm require closure and drainage; lacerations can be repaired by experienced laparoscopist
- More significant injuries are managed according to extent, location, and depth

Summary

- Timely referrals to multidisciplinary team (e.g. gynecologic endoscopist, colorectal surgeon, urologist) can reduce risk and facilitate effective treatment; advanced surgical skills and anatomical knowledge are required for deep resection and should be primarily performed in tertiary referral centers
- Careful pre-operative planning, informed consent, videoregistration of benefit to both surgeon and patient
- Meticulous adherence to 'best practice' techniques is requisite to reduce morbidity and ensure effective management of complications
- Although excision is technically demanding, operative complications remain at low risk
- Complete excision of deep disease is essential to improve symptomatology and reduce recurrence

REFERENCES

The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

Charles E. Miller, MD, FACOG

Objectives
1. List three different methods for the treatment of deep infiltrative endometriosis involving the rectum.
2. List three reasons why literature related to deep infiltrative endometriosis is difficult to interrupt.
3. Discuss the quality of life following bowel resection.

Pain descriptions reported by 113 women with endometriosis and 36 women with an apparently normal pelvis

Associations between pain area and site of endometriosis in 113 women with endometriosis
The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

• Effect of surgery for stage I – IV disease: non-comparative studies
  - Shakiba (2008)
    • Relative risk of repeat surgery
      - Age 15–29: 1.75 – 4.79
      - Age 30–39: 1
    - Surgery Free at:
      - 10–29: 63.6
      - 30–39: 88.0
      - > 40: 95.7
  - Age: 2 years 5 years 7 years
  - 10–29: 63.6 53.5 27.8
  - 30–39: 88.0 58.0 45.3
  - > 40: 95.7 78.2 76.2

The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

• Effect of surgery for stage I – IV disease: controlled studies
  - Sutton (1984)
    - Double blind study
    - 63 women with minimal/moderate endometriosis
    - Laparoscopy for pain
    - 22 laser vaporization of endometriosis plus uterosacral nerve ablation
    - 31 expectant management
    - At 6 months: 83% improved in laser group, 23% improved in expectant group
  - Sutton (1997)
    - One year follow up
    - 60 Sutton, pain relief in 50%
    - 61 Intervention to treat: success is 56% in laser group, 21% in control group
    - Absolute benefit of surgery at one year: 35%

The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

• Effect of surgery for stage I – IV disease: controlled studies
  - Jarrell (2005)
    - 29 women – mild to moderate endometriosis and severe symptoms
      - 15 laparoscopic excision
      - 14 observational laparoscopy
    - Pain diaries at baseline 3, 6, 12 months
      - No significant difference in visual analogue pain score
      - 35% reduction excision
      - 21% reduction observation
    - Similar to diaries – 42% excision, 33% observation

The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

• Effect of surgery for stage I – IV disease: controlled studies
    - 39 women laparoscopy – minimal to severe endometriosis
      - 25 excision
      - 14 expectant
    - Subsequent laparoscopy at six months to excise all lesions
    - Symptom improvement at six months – excision 80%, no treatment 0%
    - 33 women with second look – 15 excision group, 18 expectant

The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

• Effect of surgery for stage I – IV disease: controlled studies
  - Jarrell (2007)
    - Long term follow up
    - 12 – 14 years overall repeat surgery
      - 40% observational group
      - 53% excision group
      - Correlated to original pain
      - No correlation with age, stage or excision
The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

- **Excision versus ablation**
  - Wright (2005)
  - Randomized trial
  - N = 141 (mild endometriosis)
    - Follow up at six months
      - Average difference in pain score pre and post surgery
        - Excision: 11.2
        - Ablation: 8.7

- **Endometrioma surgery**
  - Beretta (1998)
  - 64 patients randomized, cystectomy versus fenestration/coagulation
  - Endometrioma > 3 cm
    - Recurrence of symptoms (months)
      - Excision = 19
      - Fenestration/coagulation = 9.5

- **According to Cochrane meta-analysis:**
  - Uterosacral ligament ablation does not improve relief due to dysmenorrhea (OR 0.77; 95% CI 0.43 – 1.39)
  - Presacral neurectomy does improve relief due to dysmenorrhea (OR 3.14; 95% CI 1.39 – 6.21)

- **Impact of modality on treatment of ovarian endometrioma**
  - Systematic literature reviews
    - Chapron (2002)
    - Vercellini (2003)
    - Hart (2005)
  - Laparoscopic excision of pseudocyst versus drainage and electrocoagulation of pseudocyst
    - Excision
      - Reduced rate of recurrence (OR 0.41; 95% CI 0.18 – 0.93)
      - Reduced rate of reoperation (OR 0.39; 95% CI 0.18 – 0.79)
      - Reduced rate of dysmenorrhea (OR 0.51; 95% CI 0.36 – 0.72)
      - Reduced rate of dyspareunia (OR 0.51; 95% CI 0.31 – 0.88)
      - Reduced rate of non-menstrual pelvic pain (OR 0.30; 95% CI 0.22 – 0.41)

- **Endometrioma surgery**
  - Alborzi (2007)
    - 100 patients randomized, cystectomy versus fenestration/coagulation
    - Recurrence of symptoms at two years
      - Excision: 11.8%
      - Fenestration/coagulation: 56.7%
  - Rate of repeat Surgery
    - Excision: 5.8%
    - Fenestration/coagulation: 22.9%

- **Zullo (2003)**
  - Randomized trial (laparoscopic presacral neurectomy and conservative surgery versus conservative surgery)
    - N = 141 (endometriosis stage 1-10)
    - Pain relief at six months
      - Laparoscopic presacral neurectomy: 87.3%
      - Conservative surgery: 62.3%
    - Pain relief at 12 months
      - Laparoscopic presacral neurectomy: 85.7%
      - Conservative surgery: 57.3%
The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

Effect of surgery for deep infiltrating disease

- Endometriosis infiltrating the vaginal and anterior rectal walls cause symptoms such as deep dyspareunia, dyschezia, and dysmenorrhea.
- Rectovaginal endometriosis has limited tendency to progress. 
  - 88 women watched for 16 years.
  - Greater than 50% had no endometriosis increase.
- Up to 16.7% of patients have deep infiltrating endometriosis in Pouch of Douglas. 
  - 3.3–12% of patients with endometriosis have deep infiltrating endometriosis of the bowel.
  - 72% have rectovaginal involvement.

Incomplete resection negatively impacts success; radical interventions increase risk of major complications, such as ureteral and rectal injuries.

• Surgical Treatment of Deeply Infiltrative Endometriosis with Deep Colorectal Involvement
  - Chapron (2006)
  - Intestinal endometriosis often multifocal and multicentric
  - N=426 (172 DIE)
    - Rectum/Rectosigmoid - 65.7%
    - Sigmoid - 17.4%
    - Cecum/ileoceleal junction - 4.3%
    - Appendix - 6.4%
    - Small Bowel - 4.7%
    - Omentum - 1.7%

Preoperative Diagnosis Using Imaging

- Transvaginal Ultrasonography
- MRI
- Excretory Urography / Uro-MRI
- Rectal Echoendoscopy

The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

Effect of surgery for deep infiltrating disease

More than 30 case series published in English peer-reviewed journals since 2000 evaluating radical conservative surgery for rectovaginal endometriosis causing pain

- Deficiencies of studies which preclude the ability to make recommendations
  - Most studies observational, or retrospective and non-comparative
  - Numbers in studies varying widely
  - Disease extent (including depth of penetration) often not well described
  - Surgical procedures vary
  - Proportion of women undergoing colorectal surgery highly variable (i.e., aggressive vs. conservative
  - Colorectal surgery rates (bowel, distal, distant, etc.) vary significantly
  - Major intra- and post-operative complications vary – 0% to 13%
  - Follow-up varies widely
  - Discrepancies in patient outcomes not always reported
  - Surgical outcome is operator-dependent
  - Publication bias (premature, older from publishing)
  - Interpretable assessment of quality populations
  - Incorporation of diagnoses

Between a Rock and a Hard Place

Incomplete resection negatively impacts success; radical interventions increase risk of major complications, such as ureteral and rectal injuries.
The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

Effect of surgery for deep infiltrating disease

- Vercellini, et al. (2006)
  - Single controlled trial – not randomized, rather patient preference
  - N = 105 with infertility and pain
    - 63 hysterectomy
    - 44 laparotomy
      - 3 laparoscopic resection
      - 6 uterine biopsy
    - 6 segmental bladder resection
    - No recurrent intraoperative complications
    - 3 left uterinepithelial fistula – ureterolysis
  - Median follow-up: 1.9 years

- Darai, et al. (2009) – 73 patients
  - N = 41
    - 25 colorectal resection
    - 16 nodule excision
  - Results
    - No differences in recurrence
    - Symptom free at two years:
      - Colorectal Resection: 80% H, 65% D, 43% N
      - Nodule Excision: 62% H, 81% D, 69% N

- Muelemann (2011)
  - 49 studies, 3,894 patients (72.7% resection, 9.8% discs, 17.4% shaving)
  - Post-op pain - post op hormones, <50% patient based reports (<18% VAS)
  - QoL did improve, however only 4% of data was prospective
The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

Effect of surgery for deep infiltrating disease

- 70-80% short term pain relief
- Success declined with time
  - By one year many patients required analgesia or hormonal therapy 1,2,3
  - Medium term recurrence of lesions – 20% 4,5,9
  - 25% repeat surgery 5,6,8


Deep infiltrating endometriosis of the rectum

- Roman (2011)
  - No evidence to support risk of recurrences less with colorectal resection versus rectal nodule excision 7
- DeCicco (2010)
  - In 34 articles describing 1,889 bowel resections, the following was noted:
    - Level of bowel resection and size of lesion were poorly reported
    - Indications for bowel resection variable, and rarely accurate
    - Surgery duration varied widely
    - Endometriosis not always confirmed at pathologic evaluation 8


The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

Effect of surgery for deep infiltrating disease

Post Operative Complications Post Bowel Resection

- Urinary retention - most common
  - Due to damage to parasympathetic plexus – bladder denervation
  - Decreased risk with transvaginal techniques 9,10
- Rectocele/Rectal Fistula – second most common
  - Risk as high as 20%
  - Lowered risk of anal fistula not opened 7,11
- Intestinal obstruction at colostomy/ileostomy, control fistula/incarceration, bowel perforation, pelvic abscess, temporary fistulae post op bowel or unrectal fistulas


Design – Prospective
- SF – 36 health status questionnaire (preoperative and 6 months postoperative)
- N > 100

Results
- Significant improvement (p < 0.0005) in all pain related symptoms, physical and mental health
- No difference in post op SF-36 scores whether treatment via intestinal nodule shaving or segmental intestinal resection (p > 0.005)


The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

Quality of life after laparoscopic segmental rectosigmoid resection of nodule shaving for deep infiltrating endometriosis with bowel involvement

Mean (± standard deviation) preoperative and postoperative scores of the scale of SF-36

<table>
<thead>
<tr>
<th></th>
<th>BEFORE</th>
<th>AT 6 MONTHS FOLLOW-UP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 total score</td>
<td>49 ± 20</td>
<td>75 ± 12</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Physical Component Scale</td>
<td>40 ± 19</td>
<td>70 ± 17</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Physical Function</td>
<td>27 ± 28</td>
<td>96 ± 15</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Role-Physical</td>
<td>48 ± 30</td>
<td>77 ± 35</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>25 ± 25</td>
<td>68 ± 24</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mental Component Summary</td>
<td>47 ± 20</td>
<td>66 ± 17</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>52 ± 32</td>
<td>72 ± 22</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>45 ± 40</td>
<td>75 ± 20</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mental Health</td>
<td>54 ± 18</td>
<td>65 ± 15</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>General Health</td>
<td>47 ± 21</td>
<td>57 ± 19</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>


The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

Quality of life after laparoscopic segmental rectosigmoid resection of nodule shaving for deep infiltrating endometriosis with bowel involvement

Mean improvement (± standard deviation) of SF-36 scores six months after surgery

<table>
<thead>
<tr>
<th></th>
<th>INTERESTING LIFE</th>
<th>MUSCULAR ENDURANCE</th>
<th>SF-36 ENDURANCE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role Physical</td>
<td>21 ± 10</td>
<td>13 ± 10</td>
<td>15 ± 10</td>
<td>0.46</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>14 ± 15</td>
<td>10 ± 10</td>
<td>12 ± 10</td>
<td>0.04</td>
</tr>
<tr>
<td>General Health</td>
<td>21 ± 10</td>
<td>13 ± 10</td>
<td>15 ± 10</td>
<td>0.46</td>
</tr>
<tr>
<td>Vitality</td>
<td>14 ± 15</td>
<td>10 ± 10</td>
<td>12 ± 10</td>
<td>0.04</td>
</tr>
</tbody>
</table>


The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

Quality of life after laparoscopic segmental rectosigmoid resection of nodule shaving for deep infiltrating endometriosis with bowel involvement

Mean improvement (± standard deviation) of SF-36 scores six months after surgery

<table>
<thead>
<tr>
<th></th>
<th>INTERESTING LIFE</th>
<th>MUSCULAR ENDURANCE</th>
<th>SF-36 ENDURANCE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role Physical</td>
<td>21 ± 10</td>
<td>13 ± 10</td>
<td>15 ± 10</td>
<td>0.46</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>14 ± 15</td>
<td>10 ± 10</td>
<td>12 ± 10</td>
<td>0.04</td>
</tr>
<tr>
<td>General Health</td>
<td>21 ± 10</td>
<td>13 ± 10</td>
<td>15 ± 10</td>
<td>0.46</td>
</tr>
<tr>
<td>Vitality</td>
<td>14 ± 15</td>
<td>10 ± 10</td>
<td>12 ± 10</td>
<td>0.04</td>
</tr>
</tbody>
</table>


The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

Quality of life after laparoscopic segmental rectosigmoid resection of nodule shaving for deep infiltrating endometriosis with bowel involvement

Mean improvement (± standard deviation) of SF-36 scores six months after surgery

<table>
<thead>
<tr>
<th></th>
<th>INTERESTING LIFE</th>
<th>MUSCULAR ENDURANCE</th>
<th>SF-36 ENDURANCE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role Physical</td>
<td>21 ± 10</td>
<td>13 ± 10</td>
<td>15 ± 10</td>
<td>0.46</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>14 ± 15</td>
<td>10 ± 10</td>
<td>12 ± 10</td>
<td>0.04</td>
</tr>
<tr>
<td>General Health</td>
<td>21 ± 10</td>
<td>13 ± 10</td>
<td>15 ± 10</td>
<td>0.46</td>
</tr>
<tr>
<td>Vitality</td>
<td>14 ± 15</td>
<td>10 ± 10</td>
<td>12 ± 10</td>
<td>0.04</td>
</tr>
</tbody>
</table>

The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

Quality of life after segmental resection of the rectosigmoid by laparoscopy in patients with deep infiltrating endometriosis

- Design – Prospective
  - SF – 36 health status questionnaire (preoperative and 1 year postoperative)
  - N = 151

- Results
  - Significant improvement (p < 0.001) in all pain related symptoms, physical and mental health

Scores of the SF-36 questionnaire applied before and 1 year after laparoscopic treatment in 151 women with rectosigmoid endometriosis

### The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

Quality of life after segmental resection of the rectosigmoid by laparoscopy in patients with deep infiltrating endometriosis

- Prospective pathologic analysis of 45 surgical specimens of bowel endometriosis obtained by laparoscopic segmental resection of the sigmoid.
- 83.3% of lesions with effected circumference greater than 40% impacted the submucous mucosal layers of the bowel
- Proceed with bowel resection

### The Impact of Surgical Treatment of Endometriosis on Pelvic Pain

Effect of surgery for deep infiltrating bowel disease

“The choice of the best surgical approach in the management of deep infiltrating endometriosis of the rectum (DIER) is the subject of a debate that is far from being closed”
References Cont’d

Anaf V, et al., JAAGL 2001; 8: 55-60.
Epub 2008 Mar 32.
Video Assisted Laparoscopy in Treatment of Extra Pelvic Endometriosis

Camran Nezhat, MD
Clinical Professor Department of OB/GYN UCSF
Adjunct Clinical Professor Department of OB/GYN & Surgery Stanford University Medical Center
Center for Special Minimally Invasive and Robotic Surgery Palo Alto, CA
www.Nezhat.org

Objectives
- Discuss the concept of extragenital endometriosis
- Review relevant pathophysiology and anatomy of extragenital endometriosis
- Review surgical principles related to treatment of extensive extragenital endometriosis

Extragenital Endometriosis

- Most common sites
  - GI tract
  - Urinary tract
- Remote sites
  - Lungs
  - Skin
  - Nervous system
  - Retina
  - Adrenal gland

Extragenital Endometriosis

- Occurs in 1-12% of patients with endometriosis
- It can occur in the absence of visible pelvic disease
- Endometriosis has been reported in almost all body structures

Symptoms

- Pain
- Bleeding
- Organ dysfunction
- Diverse and puzzling resulting from functioning endometrial tissue or scarring in the affected site

Relation to the menstrual cycle offers a clue to the diagnosis

Bowel Endometriosis

Incidence
- Rectum and sigmoid: 76%
- Appendix: 18%
- Cecum: 5%

Nezhat et al. Endometriosis
Advanced Management & Surgical Techniques.
Incidence of Bowel Endometriosis

Redwine et al. 415/1545 (26%)
Jerby et al. 30/509 (5.9%)
Nezhat 187/3201 (5.8%)

Study of 1,573 Women treated for endometriosis
- 5.4% gastrointestinal involvement
- 65% rectum or rectosigmoid involvement

Suspect Bowel Endometriosis in the presence of:
- Palpable tumor in the rectovaginal septum
- Rectal bleeding with menses
- Constipation with menses
- Diarrhea with menses
- Pain after surgical removal of all recognizable lesions

Bowel Endometriosis Treatments:
- Segmental resection
- Disk excision
- Shaving
- Rectal wall excision
- Appendectomy

Bowel Endometriosis Treatment dependent on:
- Depth of lesion
- Location
- Experience of surgeon

Gynecologists are often uncomfortable operating on the bowel.
General surgeons may be unfamiliar with endometriosis.
Bowel Endometriosis: Preop Considerations

- Consider bowel prep in all non-emergent patients
- With fixed mucosa, full thickness penetration must be anticipated
- Deep rectosigmoid resection and anastomosis should be anticipated

Laparoscopic Treatment of Bowel Endometriosis

<table>
<thead>
<tr>
<th>Authors</th>
<th>No</th>
<th>Average Age</th>
<th>Symptoms</th>
<th>Previous Surgeries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jerby</td>
<td>30</td>
<td>34 (22-49)</td>
<td>Pain (100%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nezhat</td>
<td>187</td>
<td>35 (21-56)</td>
<td>Pain (99%)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Laparoscopic Treatment of Bowel Endometriosis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Superficial/Shaving</th>
<th>Disc Excision</th>
<th>Excision Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jerby</td>
<td>30</td>
<td>23 (77%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Nezhat</td>
<td>187</td>
<td>102 (54.5%)</td>
<td>47 (25%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Authors</th>
<th>Small Bowel</th>
<th>Cecum</th>
<th>Appendix</th>
<th>Recto-sigmoid</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jerby</td>
<td>0</td>
<td>2 (7%)</td>
<td>2 (7%)</td>
<td>10 (33%)</td>
<td>29 (93%)</td>
</tr>
<tr>
<td>Nezhat</td>
<td>7 (3.7%)</td>
<td>3 (1.6%)</td>
<td>4 (2%)</td>
<td>74 (39.5%)</td>
<td>128 (68%)</td>
</tr>
</tbody>
</table>

Urinary Tract Endometriosis

- Presents in about 20% of women with endometriosis
- Symptoms include frequency, urgency, dysuria, and hematuria

Bladder Endometriosis

- Most common site of genitourinary tract endo
- Pathological confirmation is crucial – 1 out of 15 cases of deeply infiltrating bladder endo was adenosarcoma

Ureter Obstruction with Hydroureter

- Endo of genitourinary tract is common, however, it causes compression and obstruction in <1%

Laparoscopic Treatment of Ureteral Endometriosis

- Ureterolysis
- Vaporization and excision of endometriosis
- Ureterotomy or segmental ureteral resection
- Retrograde internal ureteral stent
- One layer repair (4-0 Polydioxanone)
- Postoperative ureterogram

Urinary Tract Endo: Preop Considerations

- Urinalysis
- Preoperative cystoscopy
- IVP – if ureter involvement is suspected
- Consultation with urology

Urinary Tract Endometriosis

- Study of 28 women with deeply infiltrating urinary tract endometriosis
  - 7 Bladder endometriosis
  - 21 Ureter endometriosis
- Incidence
  - October 1989 – September 1994
  - 28 (1.3%) in 2,226 women

Inclusion Criteria

- Bladder
  - Full thickness or deep musclaris involvement
- Ureter
  - Complete or partial ureteral obstruction
  - Ureteral wall involvement

Technique – Bladder

- Full thickness resection and repair 6
- Resection without mucosa 1
- Foley catheter x 10-14 days 7
  - Cystogram prior to discontinuing foley

Bladder Endometriosis

- **Age**: 29-39 (avg. 30)
- **Pelvic pain**: 6
- **Menouria**: 1


Results – Bladder

- **Complications**: 0
- **Recurrence**: 0
- **Subsequent surgery**: 2
  - Recurrence of pelvic pain: 1
  - Endometrioma: 1


Technique – Ureter

- **Partial obstruction**: 17
  - Ureterolysis and excision of endo: 10
  - Partial wall resection: 7
  - Repair: 2
  - No repair: 5
  - Internal stent x 2-8 weeks: 13
  - Pelvic Drain: 4
- **Complete resection and reanastomosis**: 4


Ureter Endometriosis

- **Age**: 24-46 (avg. 35)
- **Pelvic pain**: 21
- **Localized pain**: 14
- **Back Pain**: 11
- **Follow-up**: 5-33 months


Results – Ureter

- **Hospital stay**: 1-6 days (avg 1.8)
- **Complication**: 1
  - Pleural effusion: 20 (95%)
- **Pain relief**: 21
- **Ureteral patency**: 20
- **Functioning kidney**: 1
- **Subsequent surgery**: 2
  - Mesothelioma: 1
  - Ovarian remnant: 1


Lung and Diaphragm Endometriosis
**Historical Perspective**

- Endometriosis of the lung parenchyma was first described by Schwarz in 1938.
- Spontaneous pneumothorax associated with menstrual cycles (catamenial pneumothorax) was described as early as 1958.

**Incidence Endometriosis Lung/Diaphragm**

- 38.8% Diaphragm affected
- 29.6% Pleura affected

**Catamenial Pneumothorax**

- 22-37% of those who present with catamenial pneumothaces have implants in the pleura or diaphragm at VATS

**Pathophysiology**

- Right-side predominance (up to 92%)

**Pathophysiology**

- Sampson's theory of retrograde menstruation along with understanding of peritoneal circulation from pelvis to right paracolic gutter allows endometrial cells to reach the right subdiaphragmatic area
- Hepatic ligaments represent barriers – favor right side
**Pathophysiology**

- Hormonal model implicates high prostaglandin F₂ at ovulation, which may result in vasospasm and associated ischemia in the lungs. This, in turn and in combination with prostaglandin-induced bronchospasm, may result in alveolar rupture and subsequent pneumothorax.

**Treatment**

- Multi-disciplinary approach
- Combined Video-assisted thoracoscopic surgery (VATS) and LSC - definitive diagnosis and surgical treatment
  - Treatment of intra-abdominal and sub-diaphragmatic endometriosis; BSO in select cases

**Diaphragmatic Endometriosis**

- 24 women underwent laparoscopic treatment of endometriosis of the diaphragm
  - 17 patients had 2-5 lesions of endo on the diaphragm <1cm
  - 7 women had numerous lesions scattered across the diaphragm
  - Lesions were bilateral in 8 patients, limited to R hemidiaphragm in 14, L hemidiaphragm in 2
  - Endo infiltrated the muscular layer of the diaphragm in 7 patients

**Liver Endometriosis**

- Extremely rare entity
- First described in 1986 by Finkel et al
- Difficult to diagnose
- Often misdiagnosed preoperatively as echinococcal or amebic cyst, pyogenic abscess, cystadenoma, hematoma, or metastatic disease

**Endometriosis of the Liver**

- Only 17 cases reported in the literature
- Age ranges from 21-62
- Lesion size ranged from 2.7-24 cm
- 16/17 patients had symptomatic RUQ pain
- Only 2/17 patients reported catamenial pain
- Only 5 cases correctly diagnosed preoperatively
- 9/17 patients had their pelvis evaluated for endometriosis
  - 6 had pelvic endometriosis
  - 8 did not have pelvis evaluated

**Prevalence**

Pathophysiology

- Many theories for the origin of hepatic endometriosis including:
  - Implantation theory
  - Coelomic theory
  - Metaplasia theory
  - Induction theory
  - Autoimmune theory

- We believe lymphovascular spread also plays a role due to intraparenchymal location in some patients.

- Right lobe predominance
  - Possibly due to clockwise peritoneal fluid flow

Liver Endometriosis

- First 15 cases reported in the literature were treated by laparotomy
- Report of 2 cases treated laparoscopically

Citations


Endometriosis of the Liver: Treatment

- 14 cases treated with laparotomy
- 1 case treated with danazol (pt declined surgery)
- 2 cases treated laparoscopically

THANK YOU!
Endometriosis: Perspectives on the Future Treatment

Delay for diagnosis

Endometriosis: Diagnosis process

Onset of the symptoms

Surgical diagnosis and treatment

6 to 10 years
Endometriosis: Diagnosis process

- 16 centers
- 10 countries
- N = 745 patients

Mouahid et al., Fertil Steril (2011)

Age of 1st pelvic symptoms

Greene et al., Fertil Steril (2009)

Onset of symptoms

Adolescents 67.1%
Adults 39.2%

Endometriosis: Progressive disease?

Age and incidence of endometriotic lesions

SUP OMA DIE


Surgery for intestinal DIE

Predictive factors for transient neurogenic bladder

Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Numeric Score</th>
<th>Yes</th>
<th>No</th>
<th>Yes vs. No</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 35</td>
<td></td>
<td>6</td>
<td>37</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>BMI &gt; 25</td>
<td></td>
<td>4</td>
<td>25</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Multiple previous surgery</td>
<td></td>
<td>10</td>
<td>62</td>
<td>38</td>
<td>45</td>
</tr>
<tr>
<td>Additional intestinal resection</td>
<td></td>
<td>2</td>
<td>12</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Colonoscopic polyps in submucosa</td>
<td></td>
<td>9</td>
<td>56</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Associated hysterectomy</td>
<td></td>
<td>4</td>
<td>25</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>N DIE lesions ≥ 4</td>
<td></td>
<td>11</td>
<td>69</td>
<td>44</td>
<td>52</td>
</tr>
</tbody>
</table>

Nephrectomy

Patients

Chapron - Dousset (2011)
Endometriosis: Perspectives on the Future Treatment

Risk of recurrences

Deep endometriosis: Recurrences after surgical treatment

53%

Endometriosis: Perspectives on the Future Treatment

Multifocal disease

Deeply infiltrating endometriosis: Location (n = 877 patients)

<table>
<thead>
<tr>
<th>Main lesion</th>
<th>N</th>
<th>USL</th>
<th>Va</th>
<th>Bi</th>
<th>In</th>
<th>Ur</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLADDER</td>
<td>66</td>
<td>2</td>
<td>9</td>
<td>5</td>
<td>5</td>
<td>66</td>
</tr>
<tr>
<td>URETER</td>
<td>56</td>
<td>5</td>
<td>10</td>
<td>34</td>
<td>10</td>
<td>94</td>
</tr>
<tr>
<td>VAGINA</td>
<td>102</td>
<td>15</td>
<td>20</td>
<td>40</td>
<td>102</td>
<td>177</td>
</tr>
<tr>
<td>INTESTINE</td>
<td>340</td>
<td>88</td>
<td>178</td>
<td>164</td>
<td>34</td>
<td>594</td>
</tr>
</tbody>
</table>

Multifocality +++

Chapron (September 2011)

Intestinal endometriosis: Anatomic distribution (n = 360 patients)

Main characteristics | N | %
|---------------------|---|---
| Unique without other DIE lesions | 35 | 9.7 |
| Multifocal intestinal DIE lesions | 175 | 48.6 |
| Associated left/ right lesions | 67 | 18.6 |

Chapron - Dousset (September 2011)

Deep endometriosis: Global approach

DIE is not « an organ pathology »
Endometriosis: Perspectives on the Future Treatment

Heterogeneous disease

Deep Endometriosis: Clinical symptoms

Endometriosis

Pelvic pain

Infertility

Deep Endometriosis: Definitions

Invasion of the muscularis propria

Endometriosis: Heterogeneity

Superficial endometriosis

Ovarian endometriomas

Deep infiltrating endometriosis

Endometriosis: Associations

OMAs

DIE

SUP

Deep endometriosis: Frequency of associated ovarian endometriomas

(n = 636 patients)

<table>
<thead>
<tr>
<th>Main lesion</th>
<th>Associated OMAs</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLADDER</td>
<td></td>
<td>15.7</td>
</tr>
<tr>
<td>URETER</td>
<td></td>
<td>44.8</td>
</tr>
<tr>
<td>INTESTINE</td>
<td></td>
<td>46.7</td>
</tr>
<tr>
<td>ULR</td>
<td></td>
<td>17.6</td>
</tr>
<tr>
<td>VAGINA</td>
<td></td>
<td>20.4</td>
</tr>
<tr>
<td>Right OMA</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Bilateral OMA</td>
<td></td>
<td>27.5</td>
</tr>
</tbody>
</table>

Deeply infiltrating endometriosis
(n = 500 patients).
Results according to the presence of OMA

<table>
<thead>
<tr>
<th>Feature</th>
<th>OMA</th>
<th>OMA +</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of DIE lesions</td>
<td>1.64 ± 1.0</td>
<td>2.51 ± 1.72</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>rAFS score</td>
<td>6.7 ± 4.9</td>
<td>28.1 ± 10.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Implants</td>
<td>16.5 ± 20.7</td>
<td>36.2 ± 28.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total</td>
<td>23.6 ± 25.7</td>
<td>65.6 ± 33.1</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

a Pearsons' Chi-square test

Endometriosis: Perspectives on the Future Treatment

Deeply infiltrating endometriosis and ovarian endometriomas

Results of hormonal treatment

Deep endometriosis: Medical treatments

Endometriosis: E and P receptors in the smooth muscle component

Endometriosis: Perspectives on the Future Treatment
Endometriosis: Perspectives on the Future Treatment

- **Delay for diagnosis**
- **Earlier diagnosis**

Future:
Importance of questioning?

Endometriosis: Management options

Endometriosis: Body Mass Index

- Lafay Pillet, Chapron et al., Hum Reprod (2012)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A No DIE</th>
<th>Group B DIE</th>
<th>p</th>
<th>OR 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of Osis</td>
<td>6 (4.6%)</td>
<td>13 (13.3%)</td>
<td>0.02</td>
<td>3.2 (1.2 - 8.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A No DIE</th>
<th>Group B DIE</th>
<th>p</th>
<th>OR 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absenteeism from school during menstruation</td>
<td>33 (25.2%)</td>
<td>37 (37.7%)</td>
<td>0.04</td>
<td>1.7 (1 - 3)</td>
</tr>
</tbody>
</table>

Chapron et al., Fertil Steril (2011)
**DIE: Importance of questioning**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
<th>OR 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription of OCPs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>because of severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary dysmenorrhea</td>
<td>15 (25.9%)</td>
<td>29 (58.0%)</td>
<td>0.001</td>
<td>4.5 (1.9 - 10.4)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>18.1 ± 3.2</td>
<td>16.5 ± 2.4</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Duration of use (years)</td>
<td>5.1 ± 3.8</td>
<td>8.4 ± 4.7</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Chapron et al., Fertil Steril (2011)

**Endometriosis and oral contraceptives**

Endometriosis

Oral contraceptives

Two conclusions

**Endometriosis: Risk factors**

**Markers of Adult Endometriosis Detectable in Adolescence**

Charles Chapron MD, Bruno Borghese MD, PhD, Isabelle Streuli MD, Dominique de Ziegler MD

Family history of endometriosis (especially in first-degree relatives)

Primary severe dysmenorrhea

Absence of family from school at time of menses

Dysmenorrhea resistant to nonsteroidal anti-inflammatory drug treatment

Noncontraceptive use of oral contraceptives for dysmenorrhea

**Endometriosis: Perspectives on the Future Treatment**

Risk of recurrences

Complete surgical exeresis

**Deep intestinal endometriosis:**

**Previous surgical history for endometriosis**

Complete surgery for low rectal endometriosis

Operative laparoscopy

Open surgery

Multiple procedures

Hysterectomy

Previous surgery for Osis 82%

Operative laparoscopy 59%

Open surgery 25%

Multiple procedures 48%

Hysterectomy 5%


Previous surgery for Endometriosis

48
Deep endometriosis: prevention of recurrences after surgical treatment

- Complete surgical excision
- Multifocality
- Preop work-up
- Surgeon's experience

Op procedure:
- Resection >> Shaving

CI for sigmoid location: 30%
Intestinal Multifocality: 50%
% of circumference affected: Lymphatic dissemination

DIE with colorectal involvement

- Bowel surgery performed
  - Bowel resection anastomosis: 737 (39.9%)
  - Full-thickness disc excision
  - Shave / superficial excision: 679 (36.8%)

DIE with colorectal involvement: postoperative recurrence

- Proven osis recurrence
  - Bowel resection anastomosis: 812, 20% (2.46)
  - Full-thickness disc excision: 865, 49% (5.66

Endometriosis: perspectives on the future treatment

- Multifocal disease
- Multidisciplinary approach

Endometriosis: centers of excellence

- Reproductive endocrinology
- Surgery
- Reproductive immunology
- Neuroendocrinology
- Pain management
- Nursing
- Anesthesia
- Psychology
- Social worker
- Support group
Painful OMAs
Necessity to reconsider the management

OMAs
VAS

« Isolated » OMAs

« Severe » OMAs

IMMUNOLOGICAL BARRIER

OMAs DIE

VAS ≥ 7

« Severe » OMAs

Instestine
Ureter
Vagina
Bladder

« Isolated » OMAs

Preoperative work-up: Imaging
Referral center

Chapron – Santulli et al., Hum Reprod (2012)

Deep endometriosis: Multidisciplinary approach

EPIDEMIOLOGY
Environmental factors

Stress

Questioning

Clinical examination

PREVIOUS EPIDEMIOLOGY
Endocrinology

Molecular biology

Endometrial biopsy

Analyses - Pathology

Earlier +++ endometriosis diagnosis

OMAs DIE

VAS

VAS GI symptoms

VAS Dysmenorrhea

Preoperative serum IL-33 levels

Santulli, Batteux and Chapron (Hum Reprod, 2012)

DIE: Biomarkers

Preoperative serum IL-33 levels

Total number of DIE lesions

Endometriosis: Perspectives on the Future Treatment

Heterogeneous disease

Endometriosis

Phenotype

Endometriosis: Epigenetic changes

Chromosomal distribution of methylated and demethylated promoter regions

DNMT3L

Endometriosis: Epigenetic changes

Genetic polymorphisms of DNMT3L Involved in Hypermethylation of Chromosomal Ends Are Associated with Greater Risk of Developing Ovarian Endometriosis

Borghese, Vaiman, Chapron

Am J Pathol (2012)
**GWAS in endometriosis**

Precise endometriosis lesions' phenotype

- **SUP**
  - OR = 2.22
  - Association avec SUP: OR = 27.6

- **OMA**
  - OR = 2.09

- **DIE**
  - OR = 2.09
  - Association avec DIE: OR = 0.9

**Borghese, Chapron et al., Mol Endocrinol 2008**

- **Borghese, Chapron et al., Hum Reprod 2008**

**Endometriosis: Perspectives on the Future Treatment**

New non hormonal medical options

Results of hormonal treatment

- Deep endometriosis
  - Mitogen-activated protein kinase inhibitors
  - Statin
  - Peroxisome proliferator-activated receptor-γ inhibitors
  - Nuclear factor-κB inhibitors
  - COX-2 inhibitors
  - Aromatase inhibitors
  - Histone deacetylase inhibitors
  - Immunomodulators
  - Antioxydants

- Anti-angiogenetic agents
  - Matrix metalloproteinases inhibitors
  - Anti-angiogenetic agents
  - Anti-angiogenetic agents

- Non hormonal treatment

**Endometriosis: New non hormonal medical options**

- Results of hormonal treatment

- Deep endometriosis
  - Mitogen-activated protein kinase inhibitors
  - Statin
  - Peroxisome proliferator-activated receptor-γ inhibitors
  - Nuclear factor-κB inhibitors
  - COX-2 inhibitors
  - Aromatase inhibitors
  - Histone deacetylase inhibitors
  - Immunomodulators
  - Antioxydants

- Anti-angiogenetic agents
  - Matrix metalloproteinases inhibitors
  - Anti-angiogenetic agents
  - Anti-angiogenetic agents

**GWAS in endometriosis**

Precise endometriosis lesions' phenotype

- **SUP**
  - OR = 2.22
  - Association avec SUP: OR = 27.6

- **OMA**
  - OR = 2.09

- **DIE**
  - OR = 2.09
  - Association avec DIE: OR = 0.9

**Borghese, Chapron et al., Mol Endocrinol 2008**

- **Borghese, Chapron et al., Hum Reprod 2008**

**Endometriosis: Perspectives on the Future Treatment**

New non hormonal medical options

Results of hormonal treatment

- Deep endometriosis
  - Mitogen-activated protein kinase inhibitors
  - Statin
  - Peroxisome proliferator-activated receptor-γ inhibitors
  - Nuclear factor-κB inhibitors
  - COX-2 inhibitors
  - Aromatase inhibitors
  - Histone deacetylase inhibitors
  - Immunomodulators
  - Antioxydants

- Anti-angiogenetic agents
  - Matrix metalloproteinases inhibitors
  - Anti-angiogenetic agents
  - Anti-angiogenetic agents

- Non hormonal treatment

**Endometriosis: New non hormonal medical options**

- Results of hormonal treatment

- Deep endometriosis
  - Mitogen-activated protein kinase inhibitors
  - Statin
  - Peroxisome proliferator-activated receptor-γ inhibitors
  - Nuclear factor-κB inhibitors
  - COX-2 inhibitors
  - Aromatase inhibitors
  - Histone deacetylase inhibitors
  - Immunomodulators
  - Antioxydants

- Anti-angiogenetic agents
  - Matrix metalloproteinases inhibitors
  - Anti-angiogenetic agents
  - Anti-angiogenetic agents

**GWAS in endometriosis**

Precise endometriosis lesions' phenotype

- **SUP**
  - OR = 2.22
  - Association avec SUP: OR = 27.6

- **OMA**
  - OR = 2.09

- **DIE**
  - OR = 2.09
  - Association avec DIE: OR = 0.9

**Borghese, Chapron et al., Mol Endocrinol 2008**

- **Borghese, Chapron et al., Hum Reprod 2008**

**Endometriosis: Perspectives on the Future Treatment**

New non hormonal medical options

Results of hormonal treatment

- Deep endometriosis
  - Mitogen-activated protein kinase inhibitors
  - Statin
  - Peroxisome proliferator-activated receptor-γ inhibitors
  - Nuclear factor-κB inhibitors
  - COX-2 inhibitors
  - Aromatase inhibitors
  - Histone deacetylase inhibitors
  - Immunomodulators
  - Antioxydants

- Anti-angiogenetic agents
  - Matrix metalloproteinases inhibitors
  - Anti-angiogenetic agents
  - Anti-angiogenetic agents

- Non hormonal treatment

**Endometriosis: New non hormonal medical options**

- Results of hormonal treatment

- Deep endometriosis
  - Mitogen-activated protein kinase inhibitors
  - Statin
  - Peroxisome proliferator-activated receptor-γ inhibitors
  - Nuclear factor-κB inhibitors
  - COX-2 inhibitors
  - Aromatase inhibitors
  - Histone deacetylase inhibitors
  - Immunomodulators
  - Antioxydants

- Anti-angiogenetic agents
  - Matrix metalloproteinases inhibitors
  - Anti-angiogenetic agents
  - Anti-angiogenetic agents
The rate of proliferation of endometriotic cells is increased through the activation of the ERK pathway as a consequence of high constitutive endogenous oxidative stress.

Quantitative analysis: Optic density ratio pERK/ERK

Histological score:
- Control: 2.0 ± 0.25
- NAC: 1.19 ± 0.13

p < 0.05

Endometriosis: Oxidative stress

ROS

Activation de pERK

pERK inhibitor

Proliferation

Quantitative analysis: Optic density ratio pERK/ERK

Histological score:
- Control: 2.0 ± 0.25
- NAC: 1.19 ± 0.13

p < 0.05

Endometriosis: Role of protein kinase inhibitors

Untreated

Striatal

Untreated

Epithelial

In vivo with mouse model:
Pathology score

***: p < 0.01

Cellular production of ROS: basal levels

Deep endometriosis: Oxidative stress

DIE cells

proliferation

O2

H2O2

NO

Leconte, Dousset, Chapron and Batteux, Am J Pathol (2011)
Deep Endometriosis: Oxidative stress

**Effects on N-Acetyl-L-Cysteine: Antioxidant molecule**

Leconte, Dousset, Chapron and Batteux, Am J Pathol (2011)

Deep Endometriosis: Oxidative stress

ERK

pERK

DIE cells proliferation is increased through the activation of the ERK pathway, as a consequence of high constitutive endogenous ROS production

Leconte, Dousset, Chapron and Batteux, Am J Pathol (2011)

Deep Endometriosis: Oxidative stress

**Future +++**

ROS

Activation de pERK

pERK inhibitor

Proliferation

Leconte, Dousset, Chapron and Batteux, Am J Pathol (2011)

Deep Endometriosis: the mTOR/AKT pathway

AKT

pAKT

phospho-p70S6K

Quantitative analysis of AKT

Quantitative analysis of pAKT

Quantitative analysis of phospho-p70S6K

Leconte, Dousset, Chapron and Batteux, Am J Pathol (2011)

Deep Endometriosis: Effect of mTOR/AKT Inhibitor (Temsirolimus)

DIE: Effect of mTOR/AKT Inhibitor (Temsirolimus)

Effect of Temsirolimus (selective mTOR/AKT inhibitor +++)
on cell proliferation

Leconte, Dousset, Chapron and Batteux, Am J Pathol (2011)

Deep Endometriosis: Effect of mTOR/AKT Inhibitor (Temsirolimus)

DIE: Effect of mTOR/AKT Inhibitor (Temsirolimus)

Untreated

Treated (3 weeks after)

Leconte, Dousset, Chapron and Batteux, Am J Pathol (2011)
Take home messages

Management and strategy:
- Global approach
- Multidisciplinary approach
- New non hormonal treatments

Endometriosis: Perspectives on the Future Treatment

Delay for diagnosis → Earlier diagnosis
Risk of recurrences → Complete surgical exeresis
Multifocal disease → Multidisciplinary approach
Heterogeneous disease → Phenotype
Results of hormonal treatment → Non hormonal treatment
CULTURAL AND LINGUISTIC COMPETENCY

Governor Arnold Schwarzenegger signed into law **AB 1195** (eff. 7/1/06) requiring local CME providers, such as the AAGL, to assist in enhancing the cultural and linguistic competency of California's physicians (researchers and doctors without patient contact are exempt). This mandate follows the federal Civil Rights Act of 1964, Executive Order 13166 (2000) and the Dymally-Alatorre Bilingual Services Act (1973), all of which recognize, as confirmed by the US Census Bureau, that substantial numbers of patients possess limited English proficiency (LEP).

California Business & Professions Code §2190.1(c)(3) requires a review and explanation of the laws identified above so as to fulfill AAGL’s obligations pursuant to California law. Additional guidance is provided by the Institute for Medical Quality at [http://www.imq.org](http://www.imq.org).

**Title VI of the Civil Rights Act of 1964** prohibits recipients of federal financial assistance from discriminating against or otherwise excluding individuals on the basis of race, color, or national origin in any of their activities. In 1974, the US Supreme Court recognized LEP individuals as potential victims of national origin discrimination. In all situations, federal agencies are required to assess the number or proportion of LEP individuals in the eligible service population, the frequency with which they come into contact with the program, the importance of the services, and the resources available to the recipient, including the mix of oral and written language services. Additional details may be found in the Department of Justice Policy Guidance Document: Enforcement of Title VI of the Civil Rights Act of 1964 [http://www.usdoj.gov/crt/cor/pubs.htm](http://www.usdoj.gov/crt/cor/pubs.htm).

**Executive Order 13166,”Improving Access to Services for Persons with Limited English Proficiency”,** signed by the President on August 11, 2000 [http://www.usdoj.gov/crt/cor/13166.htm](http://www.usdoj.gov/crt/cor/13166.htm) was the genesis of the Guidance Document mentioned above. The Executive Order requires all federal agencies, including those which provide federal financial assistance, to examine the services they provide, identify any need for services to LEP individuals, and develop and implement a system to provide those services so LEP persons can have meaningful access.

**Dymally-Alatorre Bilingual Services Act** (California Government Code §7290 et seq.) requires every California state agency which either provides information to, or has contact with, the public to provide bilingual interpreters as well as translated materials explaining those services whenever the local agency serves LEP members of a group whose numbers exceed 5% of the general population.

~