Forty-second Annual
Postgraduate Program

October 17, 2009
Atlanta, GA

Endometriosis: In Search of Optimal Treatment

Course 4

Developed in
Cooperation with the
Endometriosis
Special Interest Group

Sponsored by the
American Society for
Reproductive Medicine

New Procedure to Obtain CME Credits

Dear Postgraduate Course Participant:

The Accreditation Council for Continuing Medical Education now requires that ASRM document learning for participants in CME programs. Thus, the procedure for claiming CME credits has changed. We ask your cooperation in following the steps below to ensure that your credits are provided correctly to you.

1. Within 3 days after the Annual Meeting you will be sent an email asking you to complete an online evaluation of this postgraduate course. A personalized Web link to the evaluation will be provided in your email. Please do not share this unique link.
2. In late November you will be sent a second email with a personalized Web link asking you to complete the post-test on the content of the course. This test is identical to the pre-test and will enable ASRM to assess the effectiveness of this postgraduate course as a learning activity. For your convenience, the test questions are printed in the course syllabus.

After both steps have been completed, you will be able to claim your CME credits and/or ACOG Cognates and receive a printable CME certificate. Please note that you must provide your 10-digit ACOG Membership Number to have your ACOG Cognates reported to ACOG.

Results of both the course evaluation and the post-test are anonymous.

Both steps must be followed completely by **December 31, 2009** in order to receive CME credits. A maximum of 6.5 CME credits can be claimed for the postgraduate course. Please be aware that some email systems flag emails with Web links as junk mail, and you may need to check your junk-email folder for your notifications.

Please DO NOT forward the links. In case of difficulty please email *pfenton@asrm.org*

********Deadline for receiving CME credits = December 31, 2009********

Continuing Medical Education

Continuing medical education is a lifelong learning modality to enable physicians to remain current with medical advances. The goal of ASRM is to sponsor educational activities that provide learners with the tools needed to practice the best medicine and provide the best, most current care to patients.

As an accredited CME provider, ASRM adheres to the Essentials and policies of the Accreditation Council for Continuing Medical Education (ACCME). CME activities now must first, address specific, documented, clinically important gaps in physician competence or performance; second, be documented to be effective at increasing physician skill or performance; and third, conform to the ACCME Standards for Commercial Support.

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

Developed in Cooperation with the

ENDOMETRIOSIS SPECIAL INTEREST GROUP

ANNUAL MEETING POSTGRADUATE COURSE

ATLANTA, GA

OCTOBER 17, 2009

"ENDOMETRIOSIS: IN SEARCH OF OPTIMAL TREATMENT"

Chair:

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Director
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All speakers at the 2009 ASRM Annual Meeting and Postgraduate Courses were required to complete a disclosure form. These disclosures were reviewed and potential conflicts of interest resolved by the Subcommittee on Standards of Commercial Support of the Continuing Medical Education Committee. The faculty has revealed the following information as potential conflicts of interest:

Dan I. Lebovic, M.D.. M.A.: World Endometriosis Research Foundation (WERF), Bayer Schering Pharma, Takeda: Research grant

Ian S. Fraser, M.D.: Bayer, Daiichi Sankyo, Organon: Research support

Sangeeta Senapati, M.D., M.S.: Intuitive Surgical: Proctor

Paolo Vercellini, M.D.: Nothing to disclose

This activity may include discussion of off-label or otherwise non-FDA approved uses of drugs or devices.

Accreditation statement:
The American Society for Reproductive Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Designation statement:
The American Society for Reproductive Medicine designates this educational activity for a maximum of 6.5 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

American College of Obstetricians and Gynecologists (ACOG)
The American College of Obstetricians and Gynecologists has assigned 6.5 cognate credits to this activity.

***

Please turn off/mute cell phones and pagers during the postgraduate course and all Annual Meeting sessions.

Thank you.

ENDOMETRIOSIS: IN SEARCH OF OPTIMAL TREATMENT

NEEDS ASSESSMENT AND COURSE DESCRIPTION

The bane of endometriosis is its incessant, recalcitrant and chronic nature. This is distressing both from the perspective of the patient suffering from the disease and for the practitioner attempting to offer options for mitigation. The challenges of treating endometriosis have yet to be conquered and this course will attempt to provide participants with the best available evidence for several angles of endometriosis.

Treatment modalities to assuage endometriotic lesions require costly, invasive surgery or medical approaches that are often counterproductive to fertility. Most drug therapies lead to cessation of menstrual cyclicity thereby delaying desired conception. Moreover, regardless of the treatment approach, endometriotic lesions spontaneously and often rapidly recur, accompanied by ongoing pain and/or infertility.

This one-day course for gynecologists and reproductive endocrinologists is designed to critically address the current knowledge of mechanisms of pain in endometriosis as well as current recommendations for surgical and medical treatment. Topics to be discussed include: (1) endometrial nerve fibers, (2) approach to treatment, including IUDs and innovative medical treatment both strictly for pain as well as with respect to fertility, (3) managing rectovaginal and bladder endometriosis, (4) relationship between endometriosis and cancer and a (4) discussion on the role of robot-assisted laparoscopy in endometriosis. Coherent summaries with key learning points will be provided and reinforced during the last session of case reports to be discussed among faculty and participants.

ACGME COMPETENCY

Patient Care
Medical Knowledge

LEARNING OBJECTIVES

At the conclusion of this course, participants should be able to:

1. Compare and contrast feasible medical and surgical therapies for endometriosis, including robotic-assisted laparoscopy.
2. Discuss the scientific basis and clinical implications of endometrial nerve fibers in endometriosis.
3. Describe the options for managing rectovaginal and bladder endometriosis.

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ENDOMETRIOSIS SPECIAL INTEREST GROUP

ANNUAL MEETING POSTGRADUATE COURSE

ATLANTA, GA

OCTOBER 17, 2009

"ENDOMETRIOSIS: IN SEARCH OF OPTIMAL TREATMENT"

Dan I. Lebovic, M.D.. M.A., Chair

Saturday, October 17, 2009

08:15 – 08:30	Course Introduction and Orientation **Dan I. Lebovic, M.D.. M.A.**
08:30 – 09:05	Endometrial Nerve Fibers in Endometriosis **Ian S. Fraser, M.D.**
09:05 – 09:15	Questions and Answers
09:15 – 09:50	Progestins/IUD as Treatment for Endometriosis **Ian S. Fraser, M.D.**
09:50 – 10:00	Questions and Answers
10:00 – 10:30	Break
10:30 – 11:05	Current/Future Medical Treatment Options **Dan I. Lebovic, M.D.. M.A.**
11:05 – 11:15	Questions and Answers
11:15 – 11:50	Endometriosis and Subfertility--Impact and Remedies Both Surgically and Medically **Dan I. Lebovic, M.D.. M.A.**
11:50 – 12:00	Questions and Answers
12:00 – 13:00	Lunch
13:00 – 13:45	Managing Rectovaginal and Bladder Endometriosis **Paolo Vercellini, M.D.**
13:45 – 14:00	Questions and Answers
14:00 – 14:45	Relationship between Endometriosis and Cancer **Paolo Vercellini, M.D.**

Saturday, October 17, 2009 (continued)

14:45 – 15:00	Questions and Answers
15:00 – 15:30	Break
15:30 – 16:05	The Role of Robot-assisted Laparoscopy in Radical Endometriosis Surgery **Sangeeta Senapati, M.D., M.S.**
16:05 – 16:15	Questions and Answers
16:15 – 16:50	Case Discussions **All Faculty**
16:50 – 17:00	Questions and Answers

COURSE INTRODUCTION AND ORIENTATION

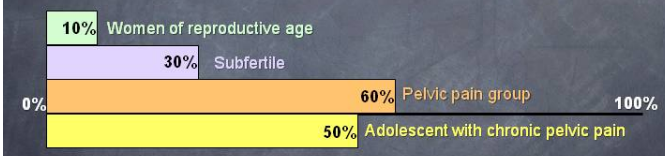
Dan I. Lebovic, M.D., M.A.
Associate Professor of Obstetrics and Gynecology
Division of Reproductive Endocrinology and Infertility
University of Wisconsin School of Medicine
Madison, Wisconsin

Endometriosis: In Search of Optimal Treatment

Course Chair:
Dan I. Lebovic, M.D., M.A. (Madison, Wisconsin, U.S.A.)
Course Faculty:
Ian S. Fraser, M.D. (Sydney, Australia)
Sangeeta Senapati, M.D., M.S. (Evanston, Illinois, U.S.A.)
Paolo Vercellini, M.D. (Milan, Italy)

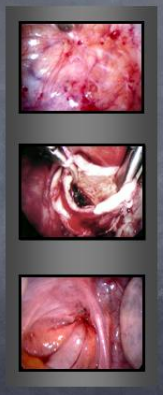
Endometriosis Prevalence

ACOG practice bulletin no.11, 1999



3 Different Entities

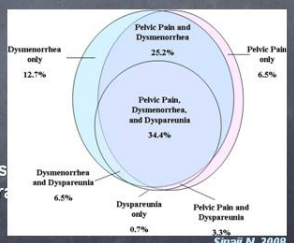
- Endometriotic implant
- Endometrioma
- Rectovaginal adenomyotic nodule



Mueller MD

Symptoms

1. **Severe dysmenorrhea**
2. Pelvic pain
3. Dyspareunia (vaginal hyperalgesia)
4. Chronic non-menstrual pelvic pain: cyclical → continuous
5. Dysuria/dyschezia
6. Decreased quality of life
7. Infertility
8. None



- Co-occurrence with: interstitial cys
  temperomandibular disorder, migra

Sinaii N, 2008

Variation in Menstrual and Reproductive Patterns

Variable	Foremothers	Modern women
Age at menarche (years)	16	12.5
Age at 1st birth (years)	19.5	24
Pregnancies (n)	6	2
Breast feeding	Years	Months
Ovulations and menstruations	50-160	450

Vercellini P, World Congress on Endometriosis, Melbourne 2008

REFERENCES

1. ACOG Practice Bulletin. Medical management of endometriosis. No. 11, 1999.
2. Sinaii N, Plumb K, Cotton L, Lambert A, Kennedy S, Zondervan K and Stratton P. Differences in characteristics among 1,000 women with endometriosis based on extent of disease. Fertil Steril 2008; 89:538-45.

ENDOMETRIAL NERVE FIBERS IN ENDOMETRIOSIS

Ian S. Fraser, M.D.
Professor of Reproductive Medicine
Department of Obstetrics and Gynaecology
Queen Elizabeth II Research Institute for Mothers and Infants
Sydney, Australia

LEARNING OBJECTIVES:
At the conclusion of this presentation, participants should be able to:

1. Specify the unique nature and clinical implications of the presence of unmyelinated nerve fibers in the myometrium, eutopic endometrium and ectopic lesions of women with endometriosis.
2. Discuss some of the complexities involved in pain generation from the pelvis and its management.
3. Describe how an endometrial biopsy for nerve fibers may be used as a diagnostic test for endometriosis.

Endometrial Nerve Fibers in Endometriosis

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DISCLOSURE

Ian S. Fraser, M.D.
Research support: Bayer, Daiichi Sankyo, Organon

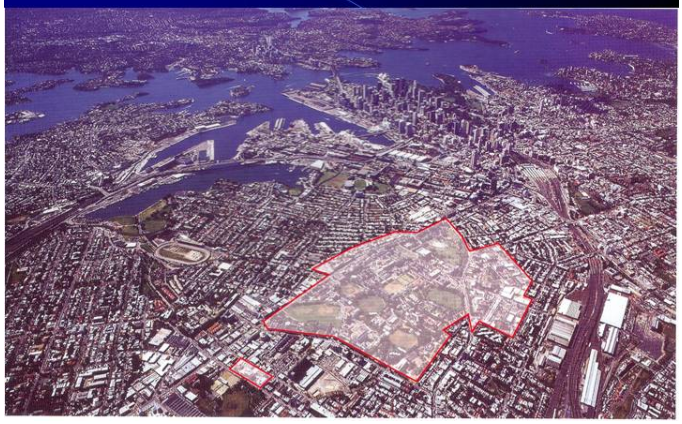
Endometrial Nerve Fibers in Women with Endometriosis

ASRM: Endometriosis Special Interest Group

Ian S. Fraser

Professor in Reproductive Medicine,
Queen Elizabeth II Research Institute for Mothers and Infants
University of Sydney
Australia

The University of Sydney



Endometriosis

- The presence of tissue, histologically similar to endometrium, outside the uterine cavity
- This tissue is functionally different from endometrium.
- The endometrium from women with endometriosis is functionally different from the endometrium of women without endometriosis.

Variability of Endometriosis

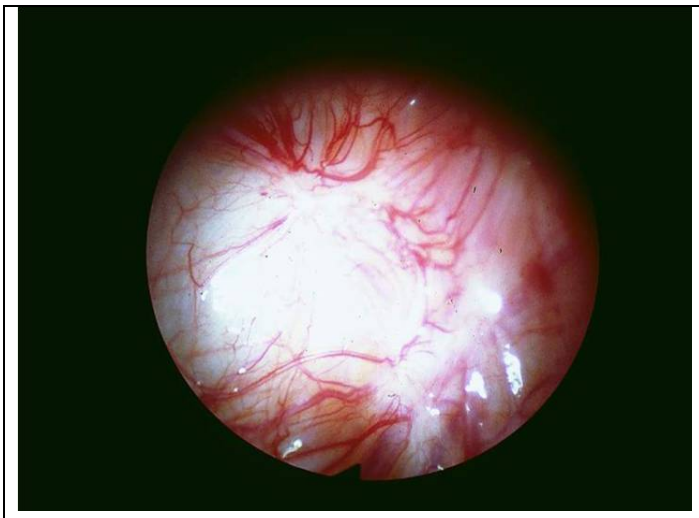
- Great variability in:
  - Clinical presentation and symptoms
  - Anatomical sites
  - Type of lesion
  - Rate of progression and spread
  - Response to treatments
  - Rate of recurrence

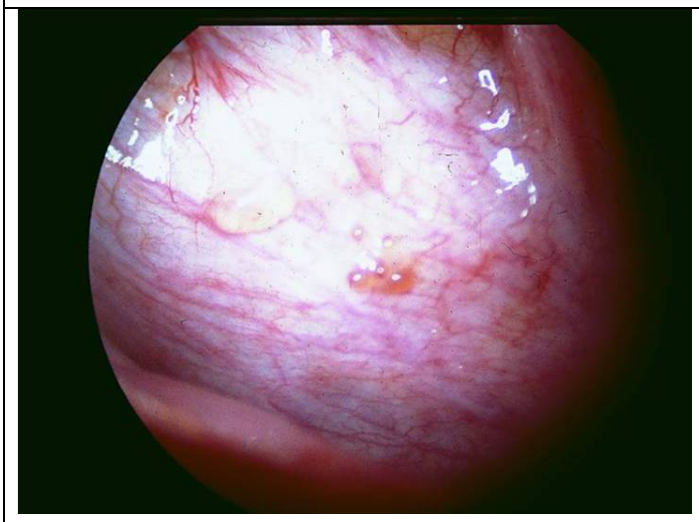
Symptoms of Endometriosis

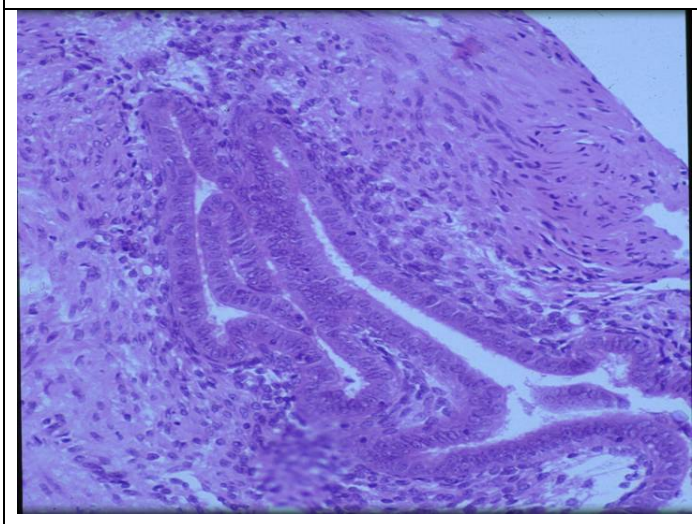
- None
- Pain
  - Secondary dysmenorrhea
  - Erratic and midcycle pain
  - Dyspareunia and bowel symptoms, painful bloating
- Menstrual
  - Premenstrual spotting or heavy bleeding
  - Vicarious menstruation
- Infertility and ?miscarriage
- (Malignant change)

Endometriosis - a Range of Pain Symptoms

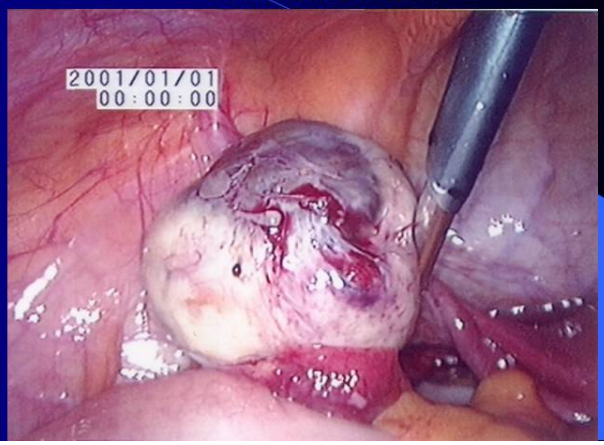
- **Menstrual cycle pain**
  - Premenstrual - general pelvic, back
  - Perimenstrual - uterine and general, back
  - Midcycle - uterine and ovarian
  - Back, leg and loin pain - referred
  - Intestinal pain - from closely located lesions
  - Peri- and post-micturition pain - from closely located peritoneal lesions or from bladder
  - From other sites
  - NO PAIN
- **Neuropathic and 'central' pain**







Left Ovarian Endometrioma after Mobilization from Pelvic Sidewall



Endometriosis Is an Endometrial Disease

- Increasing evidence suggests that endometriosis is a disease originating from abnormalities of endometrial function - and micro-structure
  (Al-Jefout et al, 2009)
- Apparent abnormalities of angiogenesis, lymph-angiogenesis (and neurogenesis)
- Multiple molecular abnormalities:
  - Structural, metabolic and immune proteins
    [Cytokeratins, integrins, heat shock proteins, actin, intracellular adhesion molecules (ICAMs), transcription factors, apoptosis, aromatase activity, oxidative pathways, etc.]
    (ten Have et al., 2008)

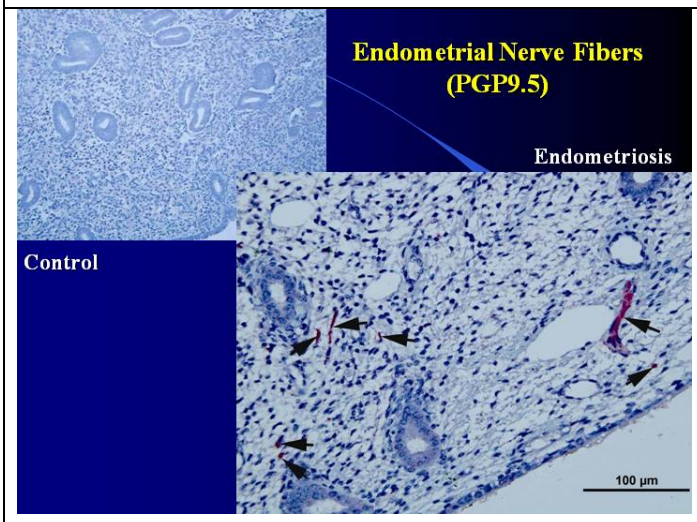
Endometrial Nerve Fibers

- We began exploring the presence of sensory nerve fibers in the endometrium and myometrium of women with complaints of pelvic pain or menstrual symptoms.
- We have made the striking observation that ALL women with endometriosis have fine, sensory or autonomic, unmyelinated nerve fibers present in the functional layer of eutopic endometrium, while women without endometriosis NEVER have these nerve fibers.

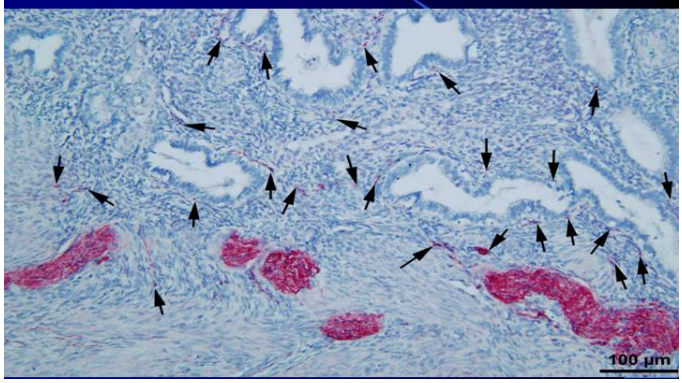
Fine Nerve Fibers in Endometrium

- Immunohistochemical localization with specific tissue markers for nerve fibers (antibodies for molecules expressed by nerve fibers)
- Pan-neuronal marker (PGP9.5) - specifically stains all nerve fibers
- Stains for myelinated nerve fibers (neurofilament NF - stains A delta fibers)
- Neurotransmitters for nerve fibers of different functions

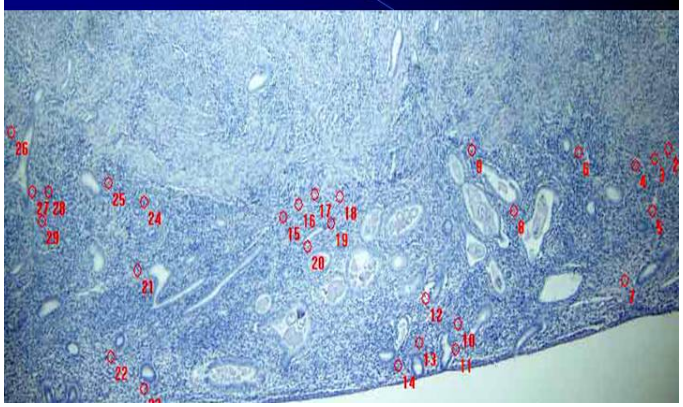
Endometrial Nerve Fibers (PGP9.5)



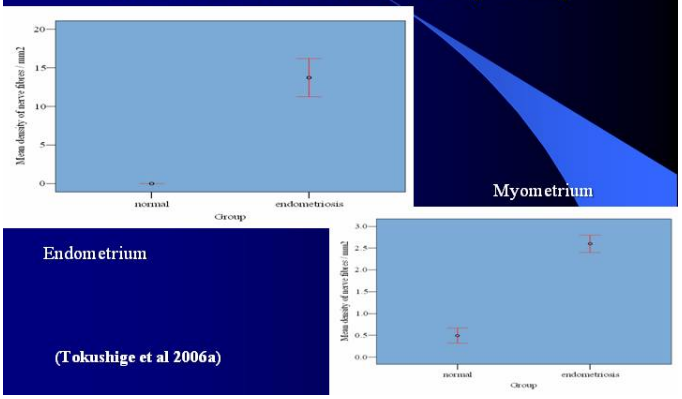
Basal Layer of Endometrium in Biopsy-confirmed Endometriosis Stained with PGP9.5 (x200).
Arrows denote small nerve fibers in deeper part of the basal layer.
Large nerve trunk visible at endometrial-myometrial interface.



Nerve Fiber Distribution in Endometrium in a Woman with Biopsy-proven Endometriosis (PGP9.5)



Mean (± SD) Density of Nerve Fibers in the Functional Layer of Endometrium and Myometrium in Women with and without Endometriosis (PGP9.5)



Identification of Nerve Fiber Types

- Identification of nerve fiber types is difficult.
- These endometrial nerve fibers are probably a combination of sensory C and autonomic C fibers.
- Sympathetic fibers strongly express neuropeptide Y (NPY), noradrenaline ("adrenergic") and adenosine triphosphate (ATP); but sometimes vasoactive intestinal polypeptide (VIP) and acetylcholine (ACh) [sympathetic fibers are controlled by cell bodies in the thoracic and lumbar regions]
- Parasympathetic fibers strongly express VIP [and co-express nitric oxide (NO) synthase] and ACh ("cholinergic"), but sometimes NPY [parasympathetic fibers are controlled by cell bodies in the cranial and sacral regions]
- Sensory fibers express substance P and calcitonin gene-related peptide (CGRP) (± NF, VIP, NPY)

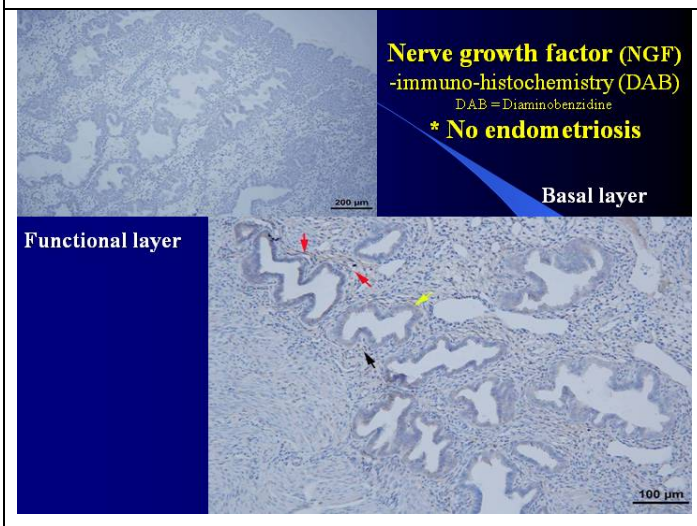
Tokushige et al. 2006b; 2007

Visceral Nerve Fiber Complexes

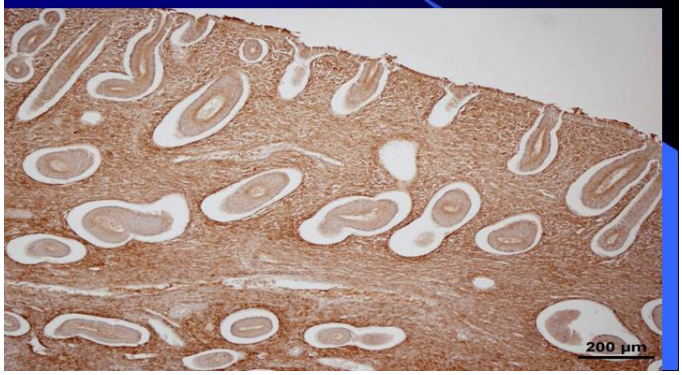
- Afferents and efferents
- Formation of plexuses
- Considerable plasticity
- Visceral sensory fibers include nociceptors, which may be polymodal
- Nociceptors may be sensitized (changed threshold) in inflammatory conditions
- Mostly unmyelinated C fibers (transmission at 1 - 2 meters per second)
- Few A delta fibers transmitting at 10 meters/second

Nociceptors

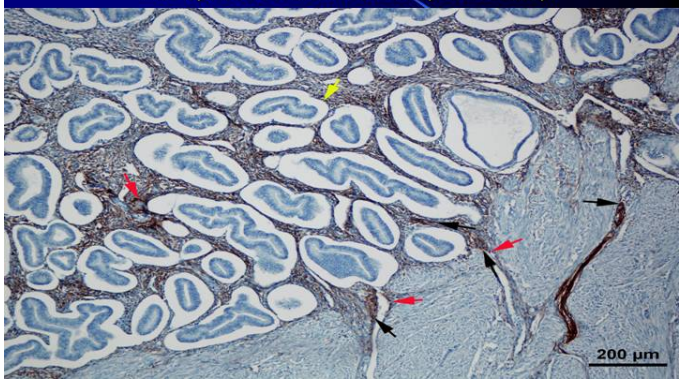
- 'Silent' receptors which do not respond to 'normal' stimuli
- Are sensory nerve fiber receptors responsive to noxious stimuli - stimuli that have the potential to do harm; trigger a reflex
- Send signals that initiate the sensation of pain
- In visceral organs they tend to respond to:
  - Excessive pressure or stretch
  - Inflammatory processes
  - A range of injurious chemical substances
  - **Sensitized by estrogen**



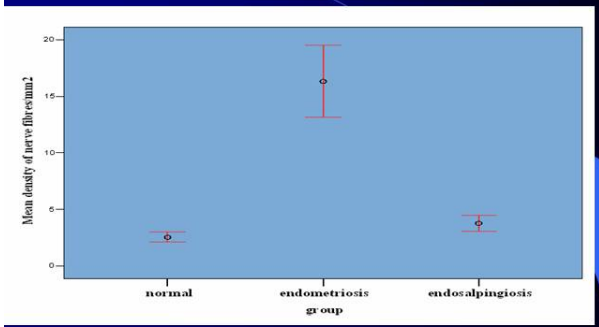
Functional Layer of Endometrium from a Woman with Biopsy-Confirmed Endometriosis Stained with NGF (x100), Showing Very Strong Positive Staining of Endometrial Glands, Stroma and Blood Vessels.



Basal Layer of Endometrium from a Woman with Biopsy-Confirmed Endometriosis Stained with NGFRp75 (x100), Showing Nerve Fibers (black arrows), Glands (yellow arrow), and Blood Vessels (red arrows).



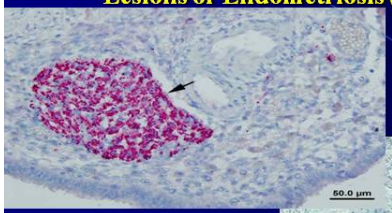
Group Comparison of Mean (±SD) Density of Nerve Fibers (PGP9.5) in Peritoneal Endometriosis, Endosalpingiosis and Normal Peritoneum.



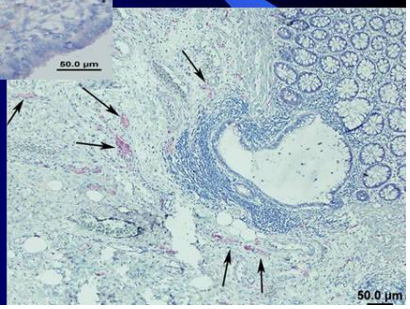
Deep pelvic nodules: mean nerve density 66.0 ± 43.5/mm² (range 2 to 300!)

(Tokushige et al, 2006b)

Nerve Fibers in Peritoneal and Deep Infiltrating Lesions of Endometriosis (PGP9.5; fast red)



Rectal lesion



Large nerve trunk (multiple different types of nerve fibers in peritoneal lesion)

Anaf et al 2000; Tokushige et al, 2006b; Wang et al, 2009

What Are These Nerve Fibers Actually Doing?

- Nociceptors for detection of painful stimuli
- What are the pain stimuli? (Berkley et al 2005)
  - Role of NGF? Prostaglandins? (both up-regulated)
  - ? Bradykinin ? Histamine (? from mast cells)
  - Sensitization by estrogen
- Autonomic fibers
  - Vascular control; muscle function
  - Epithelial secretory functions
- Unknown functions

Fascination of What May Be Happening to These Fibers During Menstruation

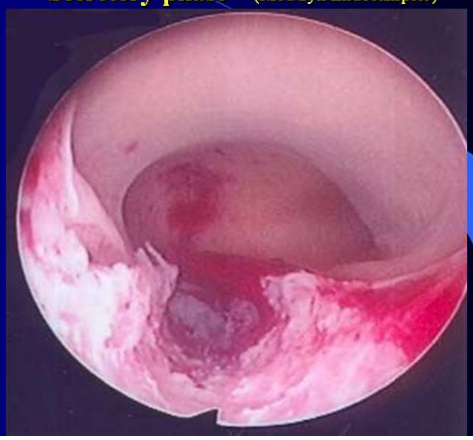
- Some fibers lie very close to the epithelial surface.
- Are these fibers damaged and partially shed, then remodel?
- Do they remain intact?
- Is there a significant re-growth each cycle?
- Are there other examples of rapid remodeling of nerve fibers?
- What do we know of nerve plexus plasticity?
- Are these nociceptors sensitized by menstrual breakdown?

Diagnosis of Endometriosis by Endometrial Biopsy: a Double-Blind Trial

- Total patients: n = 99 women (64 with endometriosis and 35 without endometriosis)
- Symptoms:
  - Pain symptoms alone (n = 52)
  - Infertility alone (n = 25; 8 with no pain)
  - Pelvic pain and infertility (n = 22)

(Al-Jefout et al, 2007; and submitted)

Hysteroscopic View after Endometrial Biopsy - Secretory phase (MedGyn Endosampler)



Overall Detection of Endometrial Nerve Fibers in Double-Blind Trial

- Small sensory C-nerve fibers were detected in 63 out of 64 women in whom endometriosis was surgically diagnosed.
- Endometrial nerve fibers were detected in 6 cases (out of 35) in whom endometriosis was not confirmed on laparoscopic inspection.
- Specificity: 83%; sensitivity 98%;
- Positive predictive value = 91%;
  Negative predictive value = 96%

(Al-Jefout et al, submitted)

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Discordant Results

- We found only one case (age 43) with no nerve fibers, but clear evidence of stage IV endometriosis at laparoscopy.
- Cases (n = 6) with positive biopsy for nerve fibers but negative endometriosis at laparoscopy:
  - Four of these cases had classic pain and infertility.
  - One case had a single spot of adhesions on the pouch of Douglas, which was not considered convincing for endometriosis.
  - One case had had endometriosis diagnosed and removed at laparoscopy seven years previously, but no evidence of active endometriosis was found at recent laparoscopy.

(Al-Jefout et al, submitted)

Implications of These Findings

- Many new directions to understand the roles and functions of these nerve fibers
- How do different nerve fibers relate to symptoms?
- What is the role of the nerve fibers in pathogenesis of endometriosis?
- What happens to them during treatment?
- Potential for the development and delivery of long-acting nociceptor blockers
- Potential for developing a less invasive means of diagnosing endometriosis (than laparoscopy)
- Diagnosis of endometriosis in adolescents before typical manifestations of the disease

Conclusions

- Women with endometriosis and pelvic pain always have fine nerve fibers present in the functional layer of endometrium (and increased in myometrium).
- Women without endometriosis never have these nerve fibers.
- These nerve fibers may play a role in pain generation
- The presence of these nerve fibers may allow reliable diagnosis without recourse to laparoscopy.
- The presence of these nerve fibers may predate the development of endometriotic lesions and symptoms.
- There may be important implications for understanding the impact of treatments and for evolving new treatments.

Collaborators

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NOTES

PROGESTOGENS/INTRAUTERINE DEVICES AS TREATMENT FOR ENDOMETRIOSIS

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LEARNING OBJECTIVES:
At the conclusion of this presentation, participants should be able to:

1. Integrate the roles that progestogens may play in the range of medical therapies available to treat endometriosis.
2. Assess the potential value of different routes of progestogen delivery and their relative effectiveness.
3. Describe the mechanisms of action of progestogens in relieving endometriosis pain.

Progestogens / Intrauterine Devices (IUDs) as Treatment for Endometriosis

ASRM: Endometriosis Special Interest Group

Ian S. Fraser, M.D.

Professor in Reproductive Medicine,
Queen Elizabeth II Research Institute for Mothers and Infants
University of Sydney
Australia

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Disclosure

Ian S. Fraser, M.D.
Research support: Bayer, Daiichi Sankyo, Organon

Approach to Endometriosis Treatment

- Depends on:
  - Symptoms
  - Fertility intentions
  - Site, nature and extent of disease
  - Effects of previous treatments
  - Prior surgeries
  - Age and wishes of the patient

Endometriosis: Management Principles and Endpoints of Treatment

- Symptom relief
  - Pain
  - Other symptoms
  - Infertility
  - Prevention of recurrence
- Analgesia
- Hormonal suppression – short- and long-term
- Surgical excision - conservative or radical

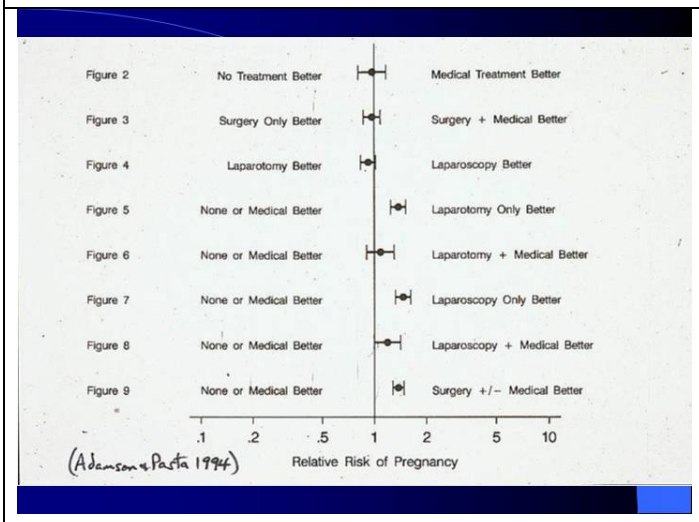
Endometriosis: Treatment

- Individualization
- Observation only
- Medical
  - Many modalities, Cochrane assessment
  - Some new and exciting ideas
- Surgical
  - Many approaches; high levels of skill
- Combinations; fertility treatments
- What about the really 'difficult' patient?

Treatment of Infertility with Endometriosis

- Meta-analyses suggest strongly that:
  - Medical treatment *per se* does not improve fertility (medical therapy may 'protect' fertility).
  - Laparoscopic or laparotomy surgery is better than medical or no treatment.
  - Combination of medical with surgical treatment counteracts benefits of surgery.
  - IVF is usually effective in presence of endometriosis.

(Adamson and Pasta 1994)



Medical "Therapies" ("Prevention" Is Better)

- GnRH analogues (or danazol)
- Combined oral contraceptives (progestogenic)
- Oral progestogens alone
- Subdermal progestogen implant (etonogestrel)
- Intrauterine progestogen
  [levonorgestrel (LNG) IUD]
- Combinations
  - levonorgesterel-releasing IUS plus etonogestrel-releasing implant
  - COC plus aromatase inhibitor (letrozole)
- Progesterone receptor modulators

"The Other Side of the Story": Surgical Treatment of Endometriosis Pain

- The size of effect of surgical interventions
- Therapeutic benefit of destruction of lesions (over diagnostic laparoscopy) 30-40% greater benefit
- Re-operation rate within 12 months = 50%
- Rectovaginal endometriosis - substantial short-term relief in 70-80%:
  - 3 - 10% major complications
  - 25% repeat surgery by 12 months
  - 50% needed analgesics or hormonal therapy by 12 months
- Expected benefit is operator-dependent

(Vercellini et al 2009)

Progestogens for Therapy of Endometriosis Pain

- Oral progestogens alone first proposed by Kistner (1958)
- Combined with estrogen in oral contraceptive: "Pseudo-pregnancy" (Kistner 1959)
- Several case series: (e.g., Luciano et al., 1988)
  - Sound benefit for majority of subjects
  - Doses often high
  - Benefit limited by side-effects
  - For maximum benefit ,need to be individualized with patience, dose-modulated (± low), long duration

Progestogens Used in Endometriosis Therapy

- Oral progestogens alone
  - MPA; norethindrone; dydrogesterone; megestrol
  - (Danazol; gestrinone)
- Oral contraceptives (COC) [why use estrogen?]
- Long-acting injections
  - Depo-medroxyprogesterone acetate
- Subdermal implants
  - Levonorgestrel

COC = combined oral contraceptives
MPA = Medroxyprogesterone acetate

Potential Mechanisms and Targets of Progestogen Action

- Suppresses ovarian follicular development (partial)
- Suppresses ovulation (dose- and patient-related)
- Direct suppressive action on endometriotic tissues and on endometrium

Potential Mechanisms of Progestogen Action on Endometrium and Lesions

- A condition with "resistance" to progestogen action (but doses used flood receptors)
- Anti-estrogen effect; (anti-proliferative; increases apoptosis)
- Reduces local inflammatory change
- Reduces nerve growth factor (NGF) expression
- Reduces angiogenesis and matrix metalloproteinase (MMP) expression

Potential Use of Combined Oral Contraceptive Pill (OCP) for Endometriosis Pain

- Continuous COC works better for pain relief in most than cyclic COC
  (Vercellini et al 2003)
- Regular post-operative use of COC effectively prevents ovarian endometrioma recurrence:
  - 36-month recurrence in never users: 49%
  - 36-month recurrence in always users: 6%
  (Vercellini et al 2008)

Persistent Pain after Surgery for Rectovaginal Endometriosis (n = 90)

- Comparison of continuous COC and low-dose oral norethisterone acetate (NET-Ac) (2.5 mg)
- No major group differences
- Satisfaction rate after 12 months was:
  - COC: 62%
  - NET-Ac: 73%

(Vercellini et al 2005)

Injectable Progestogens

- Depot-medroxyprogesterone acetate (DMPA) (intramuscular or subcutaneous)
- Probably very effective and safe, long-term (± minor bone issues)
- Limited but encouraging anecdotal data (and small case-series) for pain relief
- Clear improvement in pain intensity in comparative study:
  - Reduction of 53% in visual analog scale (VAS) scores at one year

(Walch et al 2009)

Etonogestrel-Releasing Implant (a Three-Year System)

Subdermal Progestogen Implants
(Etonogestrel-releasing)

- Several open, case series to assess implant effect on endometriosis pain
- 21 women: compared with DMPA (n=20)
  - reduction of 68% in VAS score at one year
    (Walch et al 2009)
- 50 women: VAS score reduction from 7.1 ±2.1 to 0.8 ±1.7 at three months
  - 28% amenorrhea
  - 80% satisfied or very satisfied
    (Ponpuckdee et al 2005)

Local Release of Levonorgestrel from the Intrauterine System (IUS)
(A Five-Year System)

(Nilsson et al, Contraception 1982)

Endometriosis and IUS Use

- Following conservative surgery:
  - IUD is a successful additional treatment for prevention of symptom recurrence.
- The IUD fitted in women with endometriosis:
  - Reduces dysmenorrhea and other symptoms associated with endometriosis.
  - May reduce numbers of lesions, improving staging.
  - Is effective for both peritoneal and rectovaginal lesions.
  - Is as effective as short-term gonadotropin-releasing hormon (GnRH) analogue treatment.
  - Has a high degree of patient satisfaction.

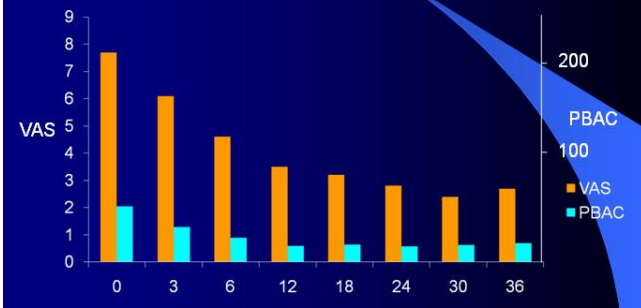
(Vercellini et al. Fertil Steril 2003; Lockhat et al. Hum Reprod 2004; Lockat et al. Hum Reprod 2005; Petta et al. Hum Reprod, 2005)

LNG-IUD for Endometriosis

- 34 women with laparoscopically confirmed endometriosis
- Prospective, observational study over 6 months
- LNG-IUD inserted
- 29 completed 6/12, and 23 (68%) continued
- Substantial improvements in severity and frequency of pain and menstrual symptoms
- Improved revised American Fertility Society (AFS) score after 6/12

Lockat, Emembolu, Konje; Hum Reprod 2004; 19: 179-184

Therapeutic Use of the IUD in Women with Endometriosis – a 3-Year Study

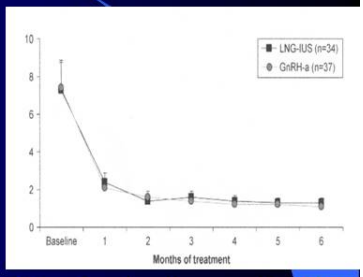


PBAC = pictorial blood loss assessment chart

Lockhat et al. Hum Reprod, 2005

LNG-IUD and GnRH Analogue (Leuprorelin) to Control Pain Due to Endometriosis

- 82 women with surgically verified endometriosis:
  - Chronic pain, VAS >3
  - Randomized for 6 months
- Significant and similar reduction in pelvic pain/quality of life (QOL)
- Stages III - IV respond better
- Amenorrhea in 78% (IUS); 98% with GnRHa at 6 months

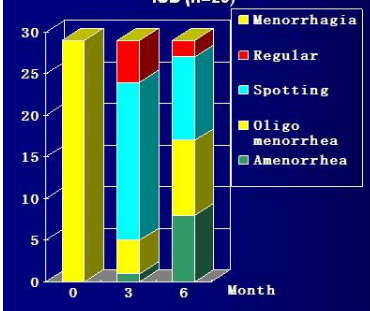


Pain: visual analogue scale (VAS)

Petta et al. Contraception 2005

Adenomyosis -related Pain and Bleeding, and the IUD

Menstrual pattern in women with adenomyosis during the use of an LNG-IUD (n=29)



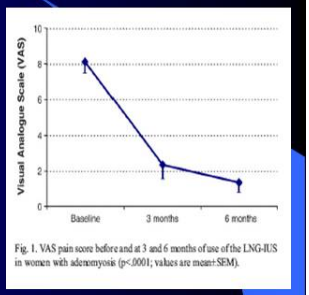


Fig. 1. VAS pain score before and at 3 and 6 months of use of the LNG-IUS in women with adenomyosis (p<.0001; values are mean±SEM).

Bragheto et al. Contraception 2007

LNG-IUD for Prevention of Recurrence of Endometriosis

- Randomized, controlled trial of expectant management or LNG-IUD insertion following laparoscopic surgery
- 40 women treated laparoscopically and then followed for 12 months
- Recurrence of moderate to severe dysmenorrhea in 10% of women with LNG-IUD and 45% of women in surgery-only group
- Significant reduction in recurrence at one year

Vercellini et al, Fertil Steril 2003; 80: 305-309

Combinations of Systems

- We have now started to use a combination of the LNG-IUD and the etonogestrel subdermal implant in difficult and poorly responsive cases
- Therapeutically logical, combining local and systemic progestogen effects using delivery systems
- Young teenager (age 15) - four previous laparoscopies - persisting symptoms causing devastation of lifestyle (Al-Jefout et al 2007)
- Now have excellent experience with 16 cases

Disadvantages of Progestogens

- Breakthrough bleeding (aim for amenorrhea)
- Breakthrough bleeding with cramps
- "Mood changes, headaches, weight gain"
- Painful abdominal bloating
- No known serious long-term complications

Effects of Hormonal Therapy on Endometrial and Endometriotic Nerve Fibers

(in Women with Some Persisting Symptoms)

- In eutopic endometrium
  - In only 3 out of 26 women were nerve fibers still detectable in the functional layer.
  - Residual nerve fibers only stained with vasoactive intestinal peptide (VIP) and neuropeptide Y (NPY)
  - very weak staining for NGF and nerve growth factor receptor (NGFR) p75
- In ectopic endometriotic tissue
  - in all of 18 peritoneal biopsies examined so far (from women on progestogens or COC), nerve fibers were still present ,but at reduced density

(Tokushige et al, Fertil Steril 2008a and b)

What Are the Implications of These Nerve Fibers for Future Treatment?

- Hormonal therapies usually suppress most endometrial nerve fibers.
- Hormonal therapies reduce but do not eliminate nerve fibers from endometriotic lesions.
- LNG-IUD very effectively suppresses endometrial nerve fibers and minimizes endometriosis recurrence.
- LNG-IUD and subdermal etonogestrel are more effective than either alone **(local and distant action)**.
- Eliminating aromatase may be of additional value.

Novel Therapies

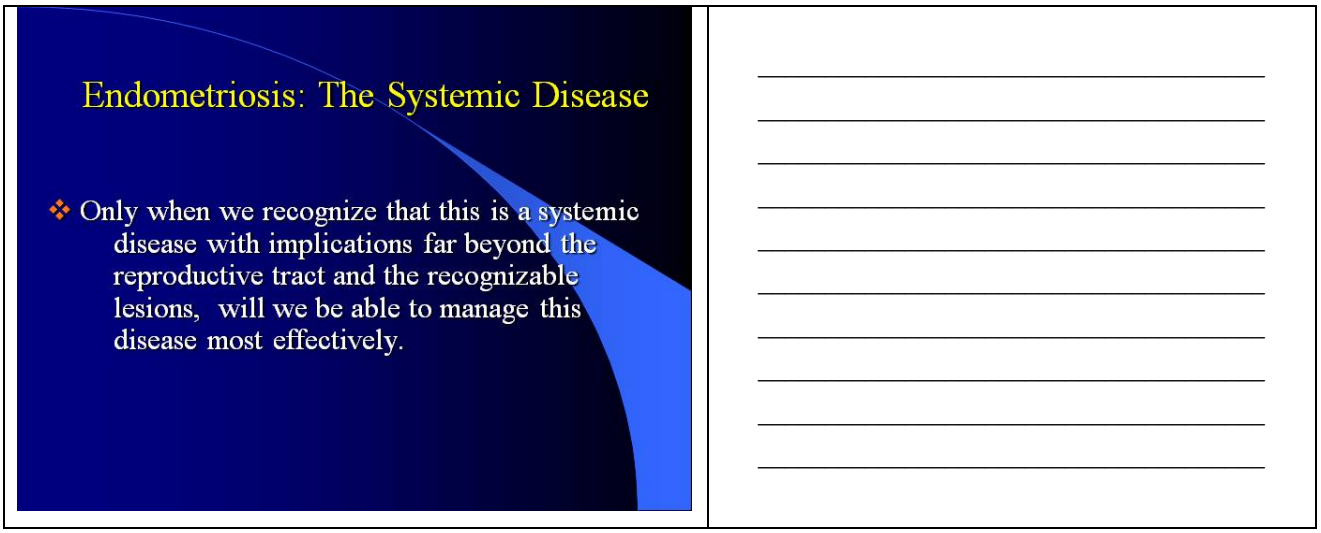
- Combination of aromatase inhibitor and progestogen (or COC)
- Combination of progestogen delivery systems
- Progesterone receptor modulators
- Immunomodulatory therapy
  - Imiquimod
  - Pentoxyphylline
- Anti-nerve growth factor agents
- Novel analgesic agents (e.g., pregabalin)

Final Issues

- Natural history of the disease
- Effective assessment
- Treatment failures
- Repeated surgery
- Long-term medical therapy
- Need for longer-term studies
- Management of infertility
- Newer therapies
- Good counseling and information

Conclusions

- Endometriosis causes more recurrent distress through pelvic pain than any other gynecological condition in Western society.
- Mechanisms of development, triggering and persistence of this pain are very poorly understood.
- The condition is very highly variable and the diagnosis is often missed.
- Some with active endometriosis have no pain.
- Management is often unsatisfactory.


Endometriosis: The Systemic Disease
Only when we recognize that this is a systemic disease with implications far beyond the reproductive tract and the recognizable lesions, will we be able to manage this disease most effectively.

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NOTES

CURRENT/FUTURE MEDICAL TREATMENT OPTIONS

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LEARNING OBJECTIVES:
At the conclusion of this presentation, participants should be able to:

1. Appraise the efficacy of oral contraceptives as a treatment choice.
2. Discuss the role of aromatase inhibitors in endometriosis.
3. Describe other options for medical management of endometriosis and soon-to-be available drugs.

Current/Future Medical Treatment Options

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Disclosure

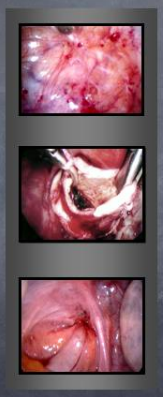
Dan I. Lebovic, MD, MA
Research support: Bayer

Outline

1. What are we treating?
2. Natural course of endometriosis
3. Standard drugs
4. Newer drug options
5. Drugs in the pipeline

3 Different Entities

- Endometriotic implant
- Endometrioma
- Rectovaginal adenomyotic nodule



Mueller, 2000

Hematogenous/Lymphatogenous Spread

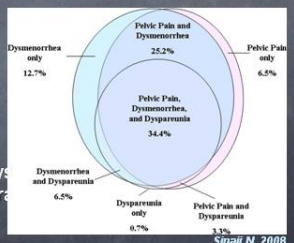
Turkcuoglu I, 2008

Clinical Presentation

What to Treat?

1. **Severe dysmenorrhea**
2. Pelvic pain
3. Dyspareunia (vaginal hyperalgesia)
4. Chronic non-menstrual pelvic pain: cyclical → continuous
5. Dysuria / dyschezia
6. Decreased quality of life
7. Infertility
8. None

- Co-occurrence with: interstitial cys
  temperomandibular disorder, migra



Sinaii N, 2008

The Need for **Better** Medical Therapy

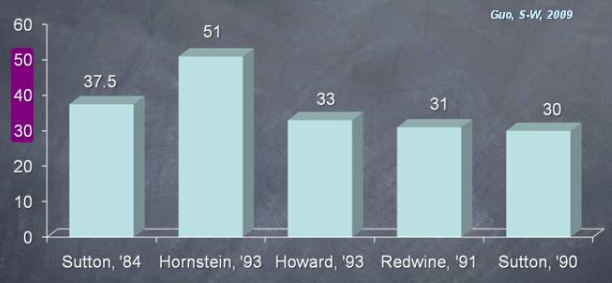
Simoens S, 2007

1. Symptoms are likely to recur following surgical or medical treatment.
2. Conception prohibited during medical treatment.
3. Co$t and side effects from medical therapy.

Natural Course of Endometriosis

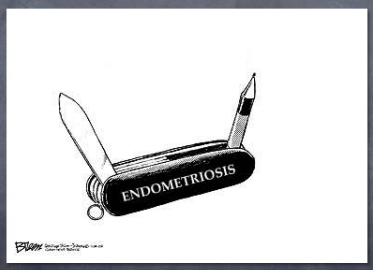
Study	▲	■	▼ [Elimination]
TOTALS, % (163)	31% (50)	31% (50)	38% (62) [23% (29)]

Pain Recurrence



- Residual disease:
  - Microscopic
  - Deep
  - Atypical lesions
  - Immunologic

Medical Treatment



Older Therapy Choices

Class	Drug	Dosage
Androgen	Danazol	400-800 mg/d po for 4-6 months
GnRH agonist	Leuprolide	1 mg SC a day
	Leuprolide depot	3.75 mg IM monthly (11.75 mg IM q 3 mos)
	Buserelin	400 µg intranasal TID
	Goserelin	3.6 mg SC monthly (10.8 mg/IM q 3 mos)
	Nafarelin	200 µg/d intranasal BID
Progestins	Gestrinone	2.5-5 mg a day
	MPA	30 mg a day po for 6 months, followed by 100 mg IM every 2 weeks x 2 months, then 200 mg IM monthly x 4 months
Oral contraceptive	Monophasic estrogen/progestin	Low ethinyl estradiol dose or the NuvaRing continuously

GnRH = gonadotropin releasing hormong; po = orally; SC = subcutaneous; IM = intramuscular; BID = twice per day; TID = three times per day; MPA = medroxyprogesterone acetate

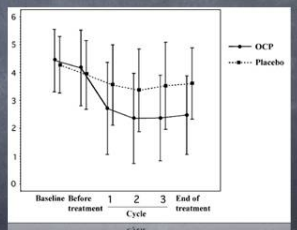
Oral Contraceptives

Endometriosis PAIN — *Harada T, 2008*

RCT study

47 Placebo ← x 4 mos → 51 COC*

Total dysmenorrhea score (m + SD)



RCT = randomized, controlled trial
COC = combined oral contraceptives

*CYCLIC ethinyl-estradiol 0.035 mg + noethisterone 1 mg

Oral Contraceptives

57 with Stage I-II Endometriosis — *Vercellini, 1993*

29 GnRH-a ← x 6 mos → 28 OCs

- Dyspareunia
- Non-menstrual pain
- Dysmenorrhea

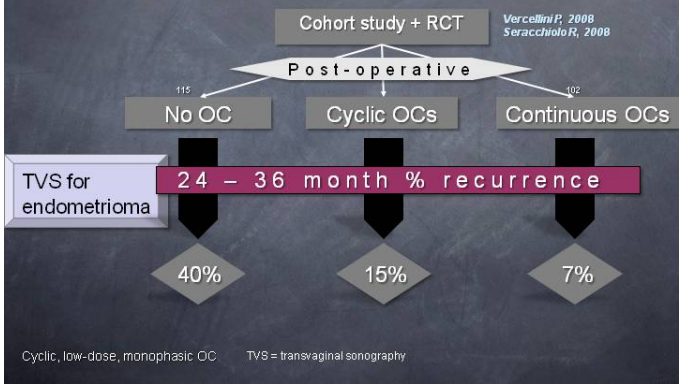
@ 6-mo → No difference

@ 12-mo → No difference

GnRH-a = gonadotropin releasing hormone analogue
OCs = oral contraceptives

Continuous may be preferable to cyclic pill regimen. *Vercellini P, 2003*

Oral Contraceptives and Endometrioma Recurrence



Newer Treatment

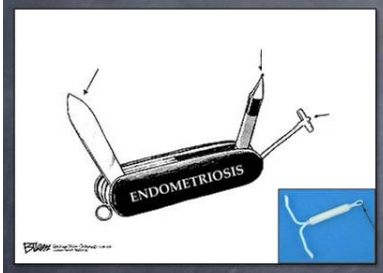
Contraceptive Patch and Ring

Surgery for stages I-IV → 12 months therapy

Vercellini P, 2009

Outcome	Patch n=84	Ring n=123
Satisfied with treatment	48%	72% ★
Withdrew	61%	36%
Amenorrhea	11%	37%
Poor bleeding control leading to change from continuous to cyclical	42%	46%

Levonorgestrel-IUD



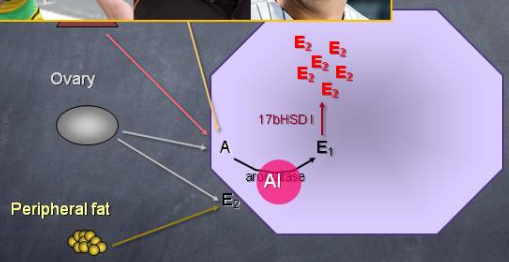
Levonorgestrel-IUD (LNG-IUD)
Fedele, 2001, Lockhat, 2004

LNG-IUD x 6 or 12 months:

- Mech: secondary oligomenorrhea, local progestin effect.
- Decreased lesions and pain from rectovaginal (RV) endometriosis.
- Equiv to GnRH agonist in randomized trial. *Petta, 2005*
- Decrease in recurrence of symptoms after having had surgery for endometriosis. *Vercellini P, 2003*

Steroidogenesis

Endometriosis



Attia, 2000
Bulun, 2000
Zeitoun, 1999

Aromatase Inhibitors

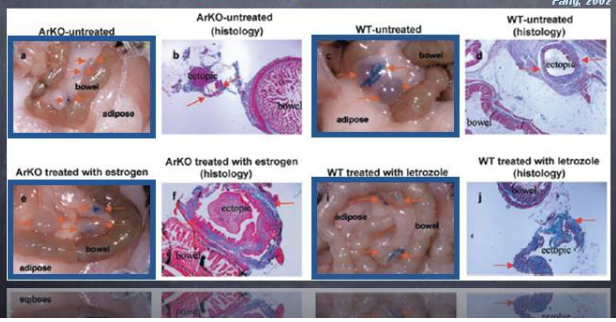
AI

Epithelial endometrial cells from women with endometriosis:

Meresman, GF, 2005

AI → ▲Apoptosis ▼Cell proliferation

Fang, 2002



Osis & Aromatase Inhibitor

10 treated medically and surgically with unsatisfactory results. Nonrandomized, pilot study

Ailawadi RK, 2004

6 mos

Dx l/s → 1 mo → Femara 2.5mg/NETAc 2.5mg/Ca-VitD → l/s

44.1	ASRM score	5.4*
6.2	Pain score	2.3*

No change in BMD

Endometriosis and Aromatase Inhibitor

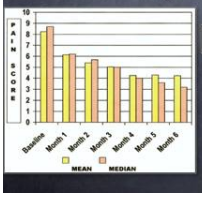
15 treated medically and surgically with unsatisfactory results
Nonrandomized, prospective study

Amsterdam, I.I., 2005

6 mos

Dx l/s → Anastrozole 1 mg + Alesse

8.2	Pain score	4.2*



14/15 significant pain reduction

No change in BMD

BMD = bone mineral density
Dx l/s = diagnostic laparoscopy

Rectovaginal Endometriosis and Aromatase Inhibitor

12 treated medically with unsatisfactory results
Nonrandomized, prospective study

Remorgida V, 2007

6 months

+ Rectovaginal endometriosis - endometrioma or bowel endometriosis* → Femara 2.5 mg/NETAc 2.5 mg/Ca-VitD → F/U

Average 7.3	VAS score	Average 2.8*

No change in BMD

Recurrence 3 months after treatment

5/12 underwent surgery

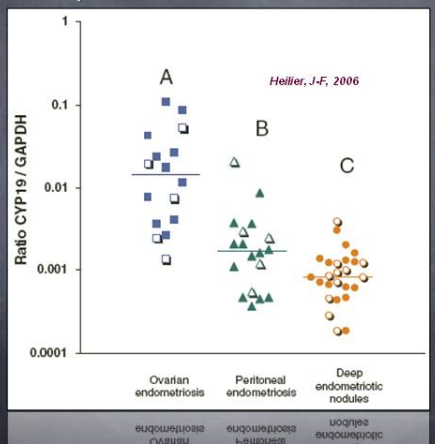
*no prior surgery

VAS = visual analogue scale
NETAc = norethindrone acetate
Ca-VitD = calcium and vitamin D

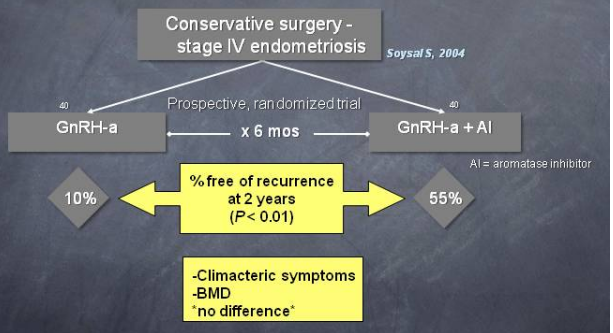
Aromatase Inhibitor (AI) Summary

- 1 RCT (post-op theory)
- 7 observational studies
- In order to reveal a small-to-medium effect of AIs (0.3 SD difference in pain scores) with α=0.05 and 80% power it would require 175 women in each group, 350 total.

Expression of Aromatase



Adjunctive Medical Treatment



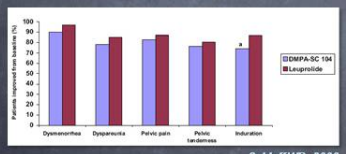
DMPA-SC 104

Endometriosis PAIN

Schlaff WD, 2006
Crosignani PG, 2006

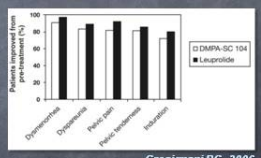
RCT study

282 DMPA-SC 104 — x 6 months — Lupron 278



Schlaff WD, 2006

EOT



Crosignani PG, 2006

DMPA-SC = depot medroxyprogesterone acetate-subcutaneous

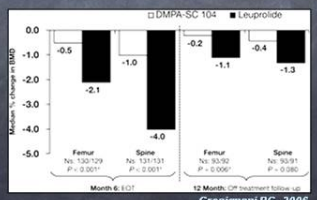
DMPA-SC 104 vs. Lupron

Adverse Effects

Schlaff WD, 2006
Crosignani PG, 2006

Adverse event	DMPA-SC 104 n=282	Lupron n=278
Headache	5.3%	8.3%
Intermenstrual bleeding	17.1%*	0.7%
Hot flushes	4.3%	14%*

Change in BMD

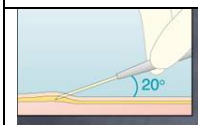


Crosignani PG, 2006

Effects on Bone Mineral Density

Treatment/condition	Duration of treatment (months)	Change in spine BMD
GnRH agonist for endometriosis	6	-4 to -10%
DMPA for endometriosis	6 12	-1.2% -2.6%
Healthy women with irregular menses	12	-1.1%
OCs in healthy women	12	0 to -1%

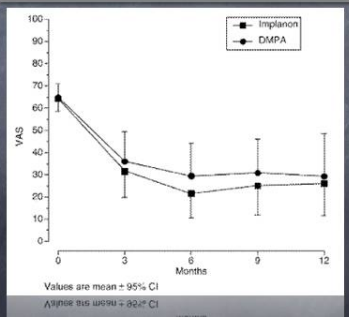
Near Future Treatment



Etonogestrel-containing Contraceptive Implant

Walch K, 2009

41 endometriosis patients
Randomized study, Implanon v. DMPA



GnRH Antagonist

15 new cases of endometriosis
Nonrandomized, pilot study

Küpker W, 2002

8 weeks

Dx l/s → 1 mo. → Cetrorelix 3 mg, once a week → l/s

60% with ASRM score improvement: average III → II

ALL reported symptom-free

Side effects:
20% - headache
20% - vaginal bleeding

Danazol Suppositories

Danazol	100 mg P.V.	400 mg P.O.
[Dz] in ovary and uterus	=	
[Dz] in serum		◀
Menstrual cycles	Normal	Abnormal

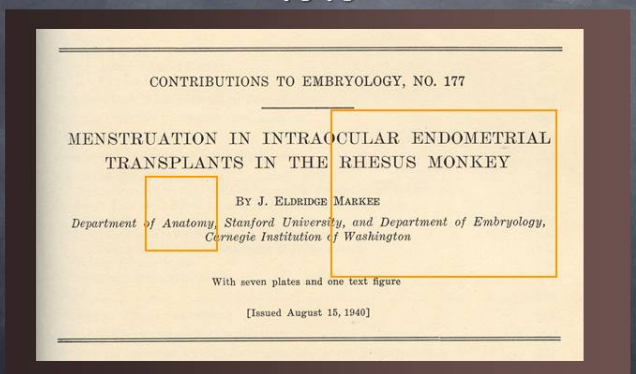
Nonrandomized, prospective study (n=21) with vaginal danazol (200 mg/d) for 12 months:

- **▼Dysmenorrhea, dyspareunia and pelvic pain.**
- **▼ Nodularity**
- **Normal menses**

Razzi S, 2007

Future Treatment

1940



CONTRIBUTIONS TO EMBRYOLOGY, NO. 177

MENSTRUATION IN INTRAOCULAR ENDOMETRIAL TRANSPLANTS IN THE RHESUS MONKEY

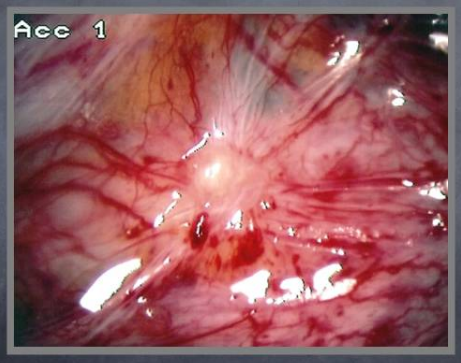
By J. Eldridge Markee

Department of Anatomy, Stanford University, and Department of Embryology, Carnegie Institution of Washington

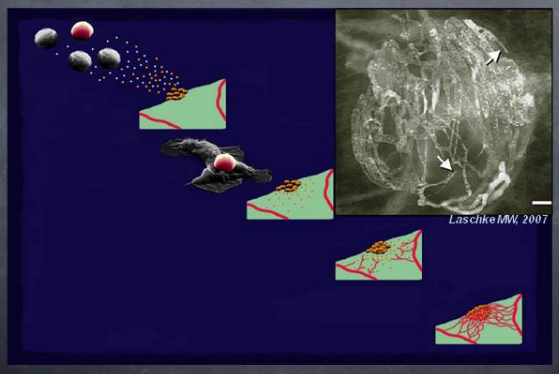
With seven plates and one text figure

[Issued August 15, 1940]

Angiogenesis

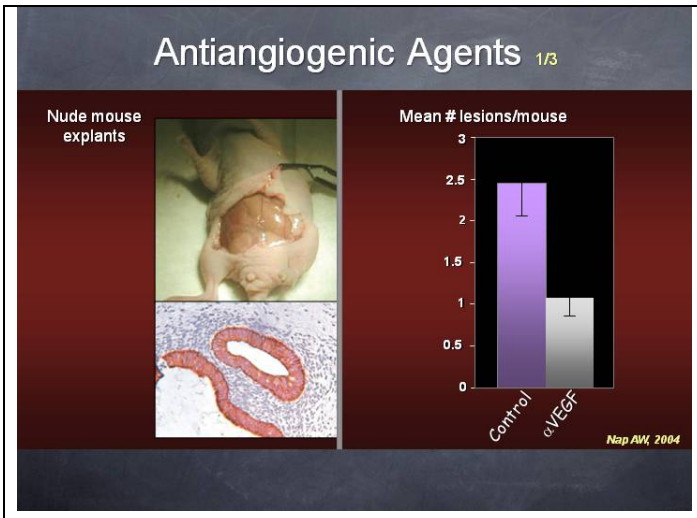


Monocyte-Endometrium Interaction

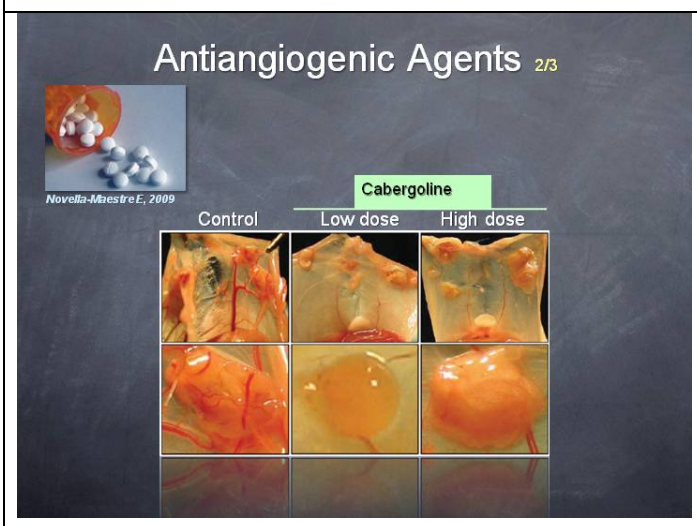


Implant Neovascularization

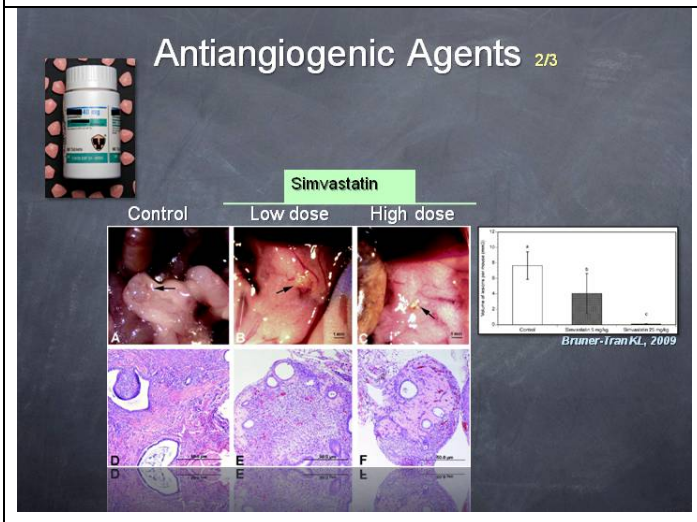
Antiangiogenic Agents 1/3



Antiangiogenic Agents 2/3



Antiangiogenic Agents 2/3



Baboon Endometriosis Model

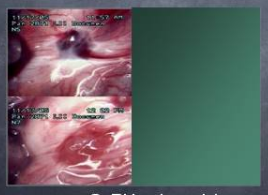
Randomized placebo-controlled trial
(placebo v. pioglitazone v. GnRH-antagonist)

Primary study endpoints:
Implant number/size/surface area

Effects of Rosiglitazone

Lebovic DI, 2007

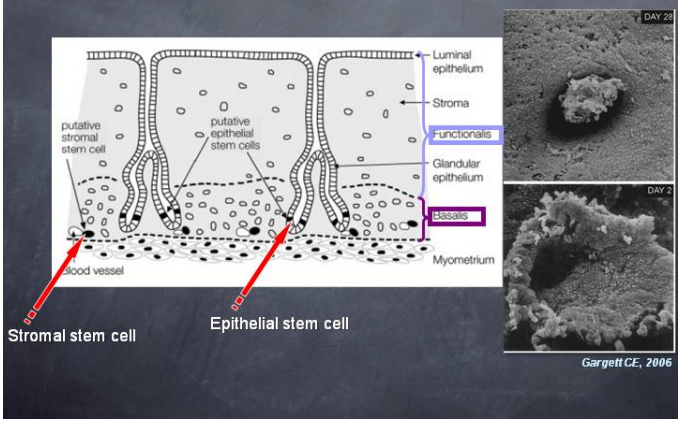
Placebo



GnRH-antagonist

Rosiglitazone

Uterine Stem Cells



Gargett CE, 2006

Uterine Stem Cells

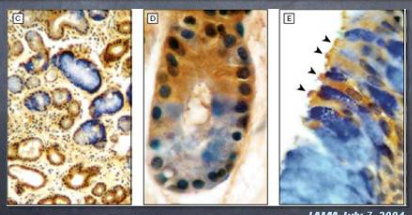
Endometrial Cells Derived From Donor Stem Cells in Bone Marrow Transplant Recipients

Hugh S. Taylor, MD

DISORDERS OF THE UTERINE endometrium are common, leading to abnormal uterine bleeding, infertil-

Context Regeneration of the endometrium in each menstrual cycle is required for reproduction. Endogenous endometrial stem cells reside in the basalis layer and serve as a source of cells that differentiate to form the endometrium. Bone marrow–derived cells have been shown to take on functions outside the hematopoietic system.

Objective To investigate the possibility that cells of extrauterine origin could repopulate the endometrium.



JAMA July 7, 2004

Storing Stem Cells from Menses

C'ELLE

Therapy Choices for Endometriosis

Class	Drug	Dosage
Androgen	Danazol	400-800 mg/day po for 4-6 months
GnRH agonist	Leuprolide	1 mg SC a day
	Leuprolide depot	3.75 mg IM monthly (11.75 mg IM q 3 months)
	Buserelin	400 µg intranasal TID
	Goserelin	3.6 mg SC monthly (10.8 mg IM q 3 months)
	Nafarelin	200 µg/day intranasal BID
GnRH antagonist	Cetrotide	3 mg SC q week

Therapy Choices for Endometriosis

Class	Drug	Dosage
Progestins	Gestrinone	2.5-5 mg a day
	MPA	30 mg a day po for 6 months, followed by 100 mg IM q 2 weeks x 2 mos, then 200 mg IM monthly x 4 mos
	Depo-medroxyprogesterone SC104	104 mg/0.65 mL SC every 3 mos
	Levonorgestrel-releasing IUS	1 x 5 years
	Etonogestrel-releasing implant	1 x 3 years
Oral contraceptive	Monophasic estrogen/progestin	Low ethinyl estradiol dose or the NuvaRing continuously
Aromatase inhibitors	Femara (Vit D, Ca^{2+}, NET-Acetate)	Femara™ 2.5 mg PO a day NET-Ac 2.5 mg a day Vit D (800 IU qd) + Ca^{2+} (1.25 gm qd)

Future Therapy Choices

Drug class	Stage of development
Selective progesterone receptor modulators	Asoprisnil-phase II J-956-phase II Dienogest-phase III
~~**Selective estrogen receptor modulators**~~	~~Raloxifene – failed clinical study~~
Estrogen receptor-β (ERB) agonists	ERB-041-preclinical
Anti-angiogenic agents	TNP-470-preclinical Endostatin-preclinical Anginex-preclinical Anti-VEGF antibodies-preclinical Rapamycin-preclinical

Future Therapy Choices

Drug class	Stage of development
TNF-α inhibitors	r-hTBP1-preclinical c5N-preclinical Onercept-phase I
Antibacterials	Doxycline-preclinical
PPAR-γ agonists	Pioglitazone-phase II
Immunomodulators	Leflunomide-preclinical
Statins	Atorvastatin-preclinical
Oral GnRH-antagonists	Elagolix-phase II

TNF = tumor necrosis factor
PPAR-γ = peroxisome proliferator-activated receptor gamma

Thank you

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NOTES

ENDOMETRIOSIS AND SUBFERTILITY—IMPACT AND REMEDIES BOTH SURGICAL AND MEDICAL

Dan I. Lebovic, M.D., M.A.
Associate Professor of Obstetrics and Gynecology
Division of Reproductive Endocrinology and Infertility
University of Wisconsin School of Medicine
Madison, Wisconsin

LEARNING OBJECTIVES:
At the conclusion of this presentation, participants should be able to:

1. Describe the possible mechanism of decreased fertility in women with endometriosis.
2. Summarize the impact of surgery on future fertility.
3. Explain the role of medical therapy with respect to fertility in endometriosis.

Endometriosis and Subfertility—Impact and Remedies Both Surgical and Medical

Dan I. Lebovic, M.D., M.A.
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Disclosure

Dan I. Lebovic, M.D., M.A.
Research support: Bayer

Outline

1. What are we treating?
2. Natural course of endometriosis
3. Standard drugs
4. Newer drug options
5. Drugs in the pipeline

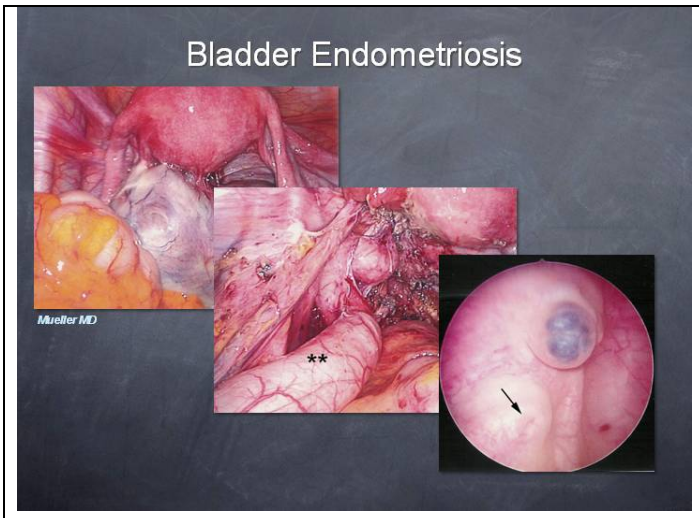
Epidemiology

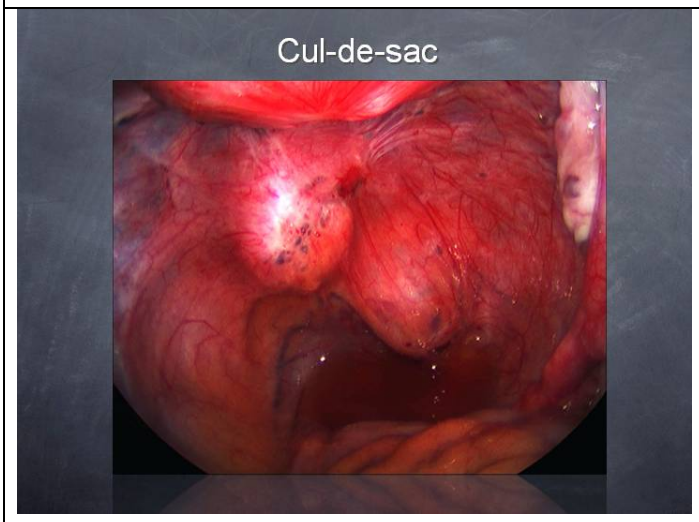
	Proven fertility	Subfertile women
Endometriosis prevalence *D'Hooghe T, 2003*	5-10%	~50%
Fecundity *ASRM2006*	15-20%	2-10%

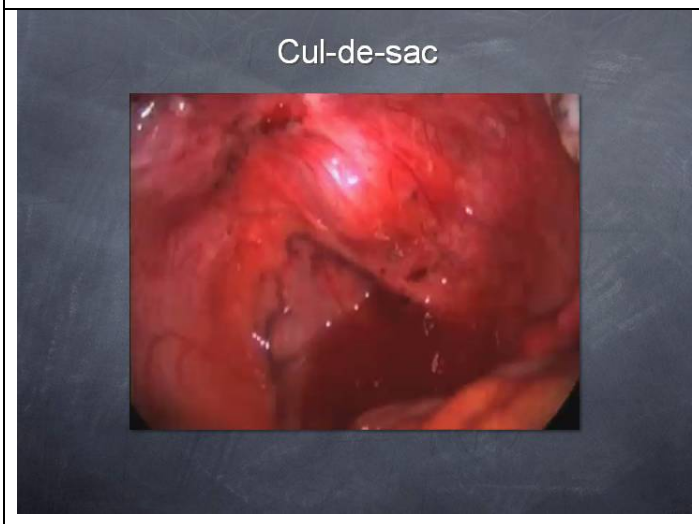
Impact of Endometriosis on Pregnancy Loss

- No evidence that endometriosis is associated with recurrent pregnancy loss.
- No evidence that medical/surgical therapy of endometriosis reduces the spontaneous miscarriage rate.

Marcoux S, 1997
Parazzini F, 1999
Vercammen EE, 2000


Bladder Endometriosis
Mueller MD
**

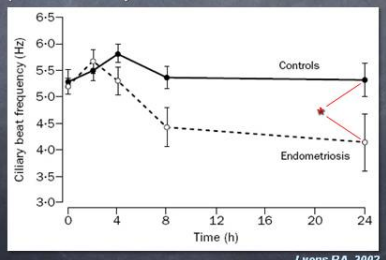

Cul-de-sac


Cul-de-sac

Treatment

Why Infertility?

- ✓ Fecundity: no endometriosis, 15-20%; with endometriosis, 2-10%.
  Hughes EG, 1993
- ✓ Altered, hostile peritoneal environment with adverse effects on oocyte, sperm, embryo, endometrium (HOXA10) or Fallopian tube function.
  Halis G, 2004, Martinez-Roman S, 1997
- ✓ Distorted pelvic anatomy.



Lyons RA, 2003

Endometriosis and Diminished Ovarian Reserve

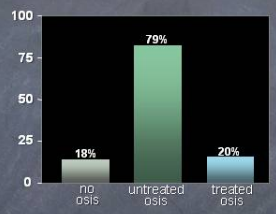
	Controls (n=75)	Endometriosis stage III-IV (n=75)
Day 3 FSH (age-matched)	9.7	12.6*

Hock DL, 2001

*$P < 0.03$

Embryo Toxicity

% with embryo- toxic peritoneal fluid (PF)



osis= endometriosis

Taketani Y, 1992

Surgical Treatment

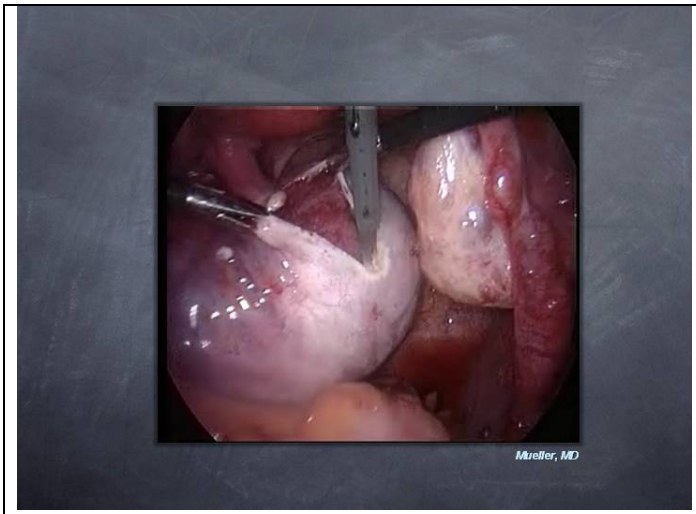
Post-surgical Ovarian Failure

Occurs in 2.4% of women who undergo cyst excision.

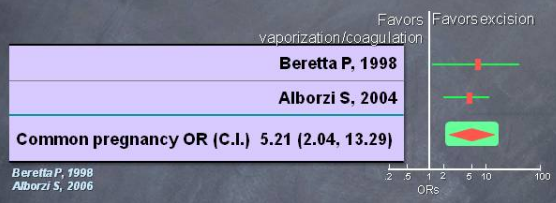
Possible causes:

1. Irreversible trauma to ovarian vascularization.
2. Excessive removal of ovarian tissue.
3. Autoimmune reaction caused by severe, local inflammatory process.

Busacca M, 2006



Surgical Technique



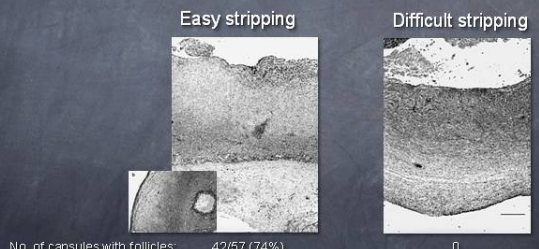
Beretta P, 1998
Alborzi S, 2006

Excisional surgery group for endometriomas >4 cm diameter:
- ► Reduced recurrence rate (x 2 years) of pelvic pain
- ► Greater rate of spontaneous conception with NNT = 2.7

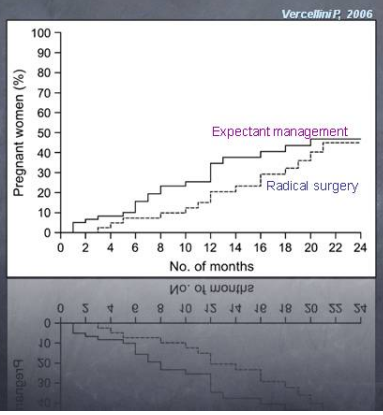
NNT = number needed to treat

Endometrioma Cystectomy

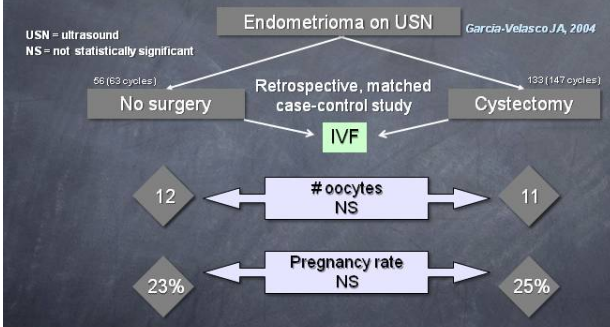
- Penetrating depths of endometrial glands ranged from 1 to 3 mm.
- The more difficult the stripping, the less likely there will be coexistent ovarian stroma in the sample. *Hachisuga, 2002*



Rectovaginal (RV) Endometriosis: Surgery for Fertility?



Endometrioma Surgery and IVF



- Note: Treatment of endometriomas does NOT impair IVF success rates.

Stage I-II and Infertility Treatment

Prospective, randomized controlled trials

"X" + IUI	n	Cycle fecundity rate: Expectant	Cycle fecundity rate: Treatment	
Clomiphene	67	3.3%	↑9.5%	Deaton, 1990
hMG, hCG	49	4.5%	↑15%	Fedele, 1992
		Live birth rate		
r-hFSH	103	2%	↑11%	Tummon, 1997

- Note: The role of unstimulated-IUI is uncertain.

hMG = human menopausal gonadotropin
hCG = human chorionic gonadotropin
r-hFSH = recombinant human follicle-stimulating hormone
IUI = intrauterine insemination

Stage I-II and Subfertility?

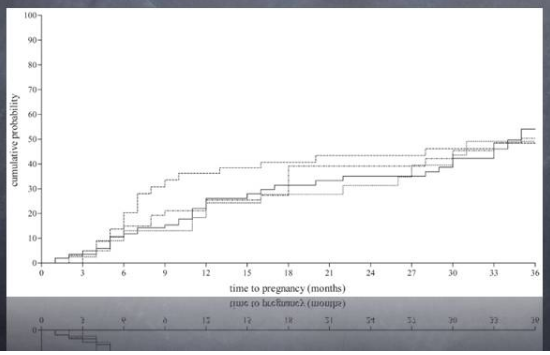
Mx = management
TDI = therapeutic donor insemination

	Monthly fecundity rate			Pregnancy rate
	Expectant Mx	IUI	TDI	Donor oocyte (IVF)
Minimal-mild endometriosis	2.5%	9%	4%	28%
Unexplained subfertility	3.5%	19%	16%	29%
	NS†	*P<0.01*	*P<0.01*	*NS*
	Berube, 1998	Omland, 1998 Nuojua-Huttunen, 1999	Hammond, 1986 Jansen, 1986 Toma, 1992	Sung, 1997

† Caveats: Placed red/white/vesicular lesions in control group; underpowered for smaller difference.

Effect of Surgery on All Stages

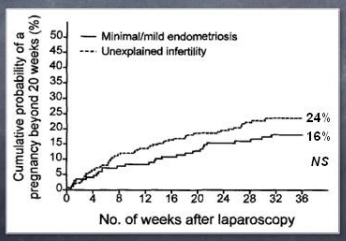
- Similar cumulative pregnancy rate for all stages after conservative surgery. *Vercellini P, 2009*



Stage I-II and Subfertility?

Prospective cohort study

	Pregnancy >20 weeks without fertility therapy
Unexplained	**23.6%**
Minimal-mild endometriosis	**15.7%**



Endometriosis and IVF

Meta-analysis of 22 studies assessing IVF outcome:
✓ Endometriosis vs. tubal factor

Barnhart K, 2002

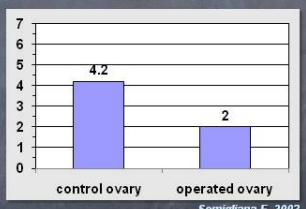
Pregnancy Rate (%)		
Stage I-II	Stage III-IV	Controls
21.1	13.8*	27.7

Significantly worse outcomes for Stage III-IV group
OR 0.46 (0.28,0.74)

Impact of Cystectomy

- 32 patients over 46 cycles who had endometriomas removed from one ovary
- 53% ↓ number of dominant follicles (IVF cycles) in ovary with prior endometrioma ($P < 0.001$)

Number of follicles with diameter >15 mm



Somigliana E, 2003

- Insufficient evidence to clarify whether the endometrioma-related damage to ovarian responsiveness precedes or follows surgery.

Garcia-Velasco JA, 2009

Laparoscopic (L/S) Ovarian Cystectomy

Effects of endometrioma size on ovulation rate

Horikawa T, 2008

	Ovulation rate (%)	
	Before surgery	After surgery
Total	34%	17%*
Endometrioma <4 cm	41%	20%*
Endometrioma ≥4 cm	27%	14%

*$P<0.01$

IVF: Pre-treatment with Gonadotropin-Releasing Hormone (GnRH) Agonist?

- 4-fold increase in clinical pregnancy with 3-6 months GnRH agonist pre-treatment; however, based on only one randomized study with small numbers.
- Endometrial $\alpha_V\beta_3$ integrin expression does not predict which endometriosis patients benefit from prolonged GnRH agonist therapy prior to IVF.

Sallam HN, 2006
Surrey ES, 2009

Oocyte Donation in Endometriosis Patients

Single donor without endometriosis	Live Birth %
Stage III-IV (n=25)	28%
No endometriosis (n=33)	27.2%

Diazl, 2000

Caveat: Could GnRH treatment affect the endometrium?

GnRH Treatment

	Epithelial endometrial cells		
	Apoptosis	IL-1β	VEGF
GnRH-agonist	74%	63%	53%
GnRH-antagonist	NS	NS	NS

Meresman, 2003

VEGF = vascular endothelial growth factor

Meta-analysis: Treatment vs. No Treatment

- ✓ Results are for 12 months of follow-up following treatment.
- ✓ Outcome measured = pregnancy rate.

	OR	95%CI
Bayer, 1988	0.61	0.24-1.54
Fedele, 1992	1.05	0.42-2.66
Telimaa, 1988	0.67	0.16-2.79
Telimaa, 1988	0.94	0.23-3.83
Thomas, 1987	1.08	0.24-4.78
Total	0.83	0.50-1.39

Hughes, 2000

- Surgery with or without post-op medical therapy → no favorable effect on fertility. *Vercellini P, 2009*

Excision of Implant

Mueller MD

Ablation Modifying Fertility? 1/3

341 with stage I-II endometriosis — *Marcoux, 1997*

L/S Ablation (172)	Diagnostic L/S only (169)
31%	18%

36-month cumulative pregnancy >20 wks probability (%) (P<0.05)

1. Need 8 surgeries to obtain 1 pregnancy (or more ?!).
2. Clear/pink vesicular lesions not considered as endometriosis.
3. Stage II - 30% in this group vs. 60% for Gruppo Italiano.
4. Monthly fecundity of L/S ablation group, 6.1% (<<20%).

Ablation Modifying Fertility? 2/3

96 with stage I-II endometriosis

Parazzini, 1999

L/S Ablation (51)	Diagnostic L/S only (46)
24%	29%

12-month cumulative conception rate (%) (*NS*)

1. Stage II - 60% in this group vs. 30% for Marcoux.
2. Power inadequate to detect the between-group difference in pregnancy rate (PR) observed in Marcoux study.
3. Secondary finding: PR for those w/ adjuvant GnRH-a therapy (39%) vs. without adjuvant GnRH-a therapy (18%) [*NS*].

Ablation Modifying Fertility? 3/3

Meta-analysis: surgery vs. no treatment (stage I-II)

Late pregnancies	Ablation	No-Ablation
Marcoux, 1997	50/172	29/169
Parazzini, 1999	10/54	10/47
Total	**OR =1.64,** 95% CI=1.02-2.67	

Crosignani PG and Vercellini P, 2000

- "Modest efficacy of endometriosis ablation in increasing the pregnancy rate in such infertile women."
- NNT = 12

Drs. Maheux and Donnez

Dr. Maheux

Dr. Donnez

Surgery for Stage III-IV

- No randomized clinical trial (RCT) or meta-analysis available to answer the question of whether surgical excision of moderate-to-severe endometriosis enhances pregnancy rate.

Adjunctive Pentoxifylline Treatment

Stage I-II, laparoscopy followed by:
± pentoxifylline

Creus M, 2008

Prospective, randomized trial

51 — No treatment — x 6 months — Pentox 800 mg/day — 47

14% — Pregnancy rate (P = 0.1) — 28%

Total # of patients required to detect	Difference in pregnancy rate
2500	5% difference
476	10% difference
282	14% difference (this study)

Note: No well controlled teratogenicity study in pregnancy

Summary Recommendations ASRM/ESHRE

- Asymptomatic women with endometriosis: surgical treatment guidelines:

Clinical condition	Recommendation
Stage I-II	Limited benefit: • Surgery recommended
Stage III-IV	Possible but unproven benefit: • Surgery recommended
Post-op adjuvant treatment	No benefit: • Not recommended
Surgery before IVF	Doubtful benefit: • Perhaps for endometrioma ≥4 cm
Recurrent endometriosis	• Not recommended

Vercellini P, 2009

Thank you

Case #1

26-year-old nulliparous woman with 4-year duration of perimenstrual pain, severe dysmenorrhea and dyspareunia on deep penetration.

- No prior surgery.
- USN: 4-cm endometrioma in right ovary; 5-cm endometrioma in left ovary.

What is your plan?

MEDICAL or SURGICAL?

- Bowel prep?
- Laparoscopy?
- Management of cysts?
- Post-op medical therapy?

Case #2

32-year-old G_2S_2 with history of STAGE I endometriosis 3 years ago; no pain at present but unable to conceive x 1 year.

- USN: Unremarkable.
- Physical: Unremarkable.

What is your plan?

MEDICAL or
FERTILITY DRUGS or
SURGICAL?

Case #3

43-year-old $G_3P_2S_1$ with 3 years' duration of perimenstrual pain, severe dysmenorrhea without help from GnRH-agonists or contraceptives. Desperate for pain relief.

- USN: Unremarkable.
- No further children desired.
- Physical: Tenderness to deep palpation.

What is your plan?

MEDICAL or SURGICAL?.

- Type of surgery?
- Type of medical therapy?

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NOTES

MANAGING RECTOVAGINAL AND BLADDER ENDOMETRIOSIS

Paolo Vercellini, M.D.
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Milan, Italy

LEARNING OBJECTIVES:
At the conclusion of this presentation, participants should be able to:

1. Define the pathogenetic principles on which to base a safe and effective surgical approach to rectovaginal and bladder endometriosis.
2. Recommend a selective preoperative diagnostic work-up.
3. Describe the most commonly adopted techniques to deal with these demanding disease forms.

Managing Rectovaginal and Bladder Endometriosis

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Disclosure

Paolo Vercellini, M.D.
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ANNUAL MEETING POSTGRADUATE COURSE
ATLANTA, GA. 2009
"ENDOMETROISIS: IN SEARCH OF OPTIMAL TREATMENT"

Managing Rectovaginal and Bladder Endometriosis

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Pathogenic Pathway Leading to Anatomic Distortion

1. Superficial implantation of endometrial cells
2. Strong inflammatory stimulus
3. "Protective" response with adhesion of pelvic structures to exclude the irritating lesion from the peritoneal environment
4. Fibroblast participation in the "burial" of endometriotic foci
5. Scar retraction
6. Duplication and invagination of adjacent surfaces

Managing Rectovaginal Endometriosis

The postero-uterine pouch is the most frequent site of deep endometriosis. Generally, the left hemipelvis is particularly involved, and dense, diffuse adhesions cause tenacious coalescence of several organs.

The sigmoid colon may adhere to the tube, ovary and left broad ligament, burying the adnexa partially or completely. The rectum obliterates the pouch of Douglas, rendering recognition of the left uterosacral ligament difficult. Frequently, the posterior vaginal fornix is also infiltrated.

Posterior cul-de-sac deep endometriosis is usually associated with severe pain symptoms and a substantial worsening of health-related quality of life.

From Vercellini et al., Gynecol Obstet Invest 2009

Pathogenesis of Rectovaginal Endometriosis

1. Inflammation in the most dependent portion of the pouch of Douglas
2. Adhesion between anterior rectal wall and posterior fornix
3. Fibrosis and infiltration of the muscular layers of the rectum and vagina
4. Formation of a sort of desmoid tumor, which is a fibrotic "cast" of what was the bottom of the postero-uterine pouch

Pathogenesis of Rectovaginal Endometriosis

Endometriotic plaques and nodules are found in the posterior vaginal fornix, cranially with respect to the rectovaginal septum.

Various forms of peritoneal and ovarian disease are usually present in patients with vaginal endometriosis, suggesting that the pathogenesis may not be different.

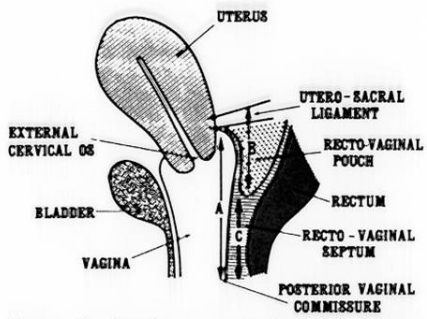


Figure 1. The dimensions measured at the time of examination under anesthesia and laparoscopy. A = length of posterior vaginal wall; B = depth of rectovaginal pouch; C = length of rectovaginal septum.

From Kuhn RJP and Hollyock VE. Obstet Gynecol 1982;59:445-447

Anatomic Dimensions of the Women Studied

	Nulliparas (n=12)	Multiparas* (n=15)
Length of posterior vaginal wall (cm)	7.5 ± 0.3	8.7 ± 0.4
Depth of rectovaginal pouch (cm)	5.3 ± 0.5	5.4 ± 0.4
Length of rectovaginal septum (cm)	2.1 ± 0.3	3.3 ± 0.5

Data are mean ± SEM
*Subjects without prolapse

Modified from Kuhn and Hollyock, Obstet Gynecol 1982

Anatomy of the Rectovaginal Pouch and Septum

"The base of the rectovaginal pouch extended to at least the level of the middle third of the vagina in 41 (93%) patients and was related to the upper third of the vagina in the remaining 3 patients."

From Kuhn and Hollyock, Obstet Gynecol 1982

Vaginal Length and Absolute and Relative Depths of the Pouch of Douglas

	Nulliparous women (n=22)	Parous women (n=28)
Total vaginal length (cm)	9.8 ± 1.1	10.1 ± 1.1
Absolute depth of Douglas pouch (cm)	4.8 ± 1.6	4.5 ± 1.8
Relative depth of Douglas pouch (%)*	49.4 ± 15.9	45.5 ± 20.2

*percentage of the pouch of Douglas with respect to total vaginal length

From Baessler & Schuessler, Am J Obstet Gynecol 2000

Clinical Characteristics and Anatomical Measurements of the 209 Women Studied

	Endometriosis with deep lesion (*n*=16)	Endometriosis without deep lesion (*n*=127)	Miscellaneous anomalies (*n*=35)	Normal pelvis (*n*=26)
Age (years)	27.5 ± 2.9	31.2 ± 3.6	31.7 ± 4.0	32.4 ± 2.5
Nulliparous	15 (83)	99 (78)	27 (77)	28 (80)
Douglas pouch depth (cm)	3.6 ± 1.6*	5.3 ± 0.8	5.2 ± 0.9	5.5 ± 0.8
Douglas pouch volume (mL)	41.6 ± 19.3*	67.2 ± 18.1	67.6 ± 12.6	65.8 ±10.9

Data are presented as mean ± SD or *n* (%)
*p <0.001, one way-ANOVA

From Vercellini et al., Fertil Steril 2000

Magnetic Resonance Imaging (MRI) and Deeply Infiltrating Endometriosis (DIE)

- 8 women with histologically confirmed DIE
- DIE nodules located below the torus uterinus, level with the posterior vaginal fornix and the upper third of the posterior vaginal wall.
- The DIE nodules were always located above the upper edge of the rectovaginal septum, with the latter appearing fine and regular.
- DIE lesions do not originate from the rectovaginal septum.

From Chapron et al., Gynecol Obstet Invest 2002

Frequency of Other Forms of Endometriosis in 93 Patients with Deep Peritoneal Endometriotic Nodules

Forms of disease	*n*	%	95% CI
Superficial peritoneal implants	57	61	51.4-71.2
Endometriotic ovarian cysts	47	51	40.3-60.7
Pelvic adhesions	69	74	65.3-83.1
Overall	87	94	87.7-97.2

From Somigliana et al., Hum Reprod 2004

Pathogenesis of Rectovaginal Endometriosis

What is called "rectovaginal septum" endometriosis may instead be massive disease of the deepest portion of the pouch of Douglas that has been buried and excluded from the remaining pelvis by adhesions.

The semilunar hard crest protruding through the posterior fornix could be the fibrotic "cast" of what was the bottom of the posterior cul-de-sac.

Managing Rectovaginal Endometriosis

History

When deep nodules of the posterior cul-de-sac are present, women usually experience organic types of pain, such as during intercourse or defecation.

Patients should be specifically questioned regarding bowel function with the objective of identifying early signs of sub-occlusion, such as colic pain before defecation and expulsion of increasingly thinner stools.

Stenosis of the rectal ampulla is exceedingly rare, and strictures usually involve the rectosigmoid junction. Accordingly, low rectal plaques generally do not cause obstruction.

Hematochezia caused by intestinal endometriosis should be differentiated from bleeding due to other causes. When episodes are cyclic and concomitant with menstruation, a bowel endometriotic lesion with mucosal infiltration is the most obvious diagnosis.

From Vercellini et al., Gynecol Obstet Invest 2009

Managing Rectovaginal Endometriosis

Diagnosis

Endometriotic plaques of the Douglas pouch are easily reached by the gynecologist's examining fingers and a careful rectovaginal evaluation is usually informative enough.

It is important to determine whether the lesion is situated in the midline or if it extends laterally, involving the parametria. From a surgical point of view, the former situations are generally easier to handle, whereas the latter may be rendered problematic by the proximity of the ureter, as well as uterine and vaginal vessels. When lateral infiltration has occurred, the left side is more often affected than the right.

Transvaginal and transrectal ultrasonography, as well as MRI, have been proposed to define the limits and degree of infiltration of these lesions.

The recent results of transvaginal ultrasonography appear promising and, if confirmed, would allow accurate identification of location and extension of deep endometriotic lesions with a readily available, simple, and well-accepted technique at limited cost.

From Vercellini et al., Gynecol Obstet Invest 2009

Managing Rectovaginal Endometriosis

Diagnosis

Preoperative rectosigmoidoscopy is suggested but, in case of dense fibrosis or large bowel nodules, the instrument may not be inserted beyond the rectosigmoid junction.

Double contrast barium enema delineates objectively the characteristics of the bowel walls and lumen, allowing simultaneous evaluation of the proximal colon. Resection can be anticipated when a stenosis reduces the lumen to < 50% of the diameter of the adjacent intestinal tracts.

An ultrasound scan of the urinary apparatus must be included in the diagnostic workup of women with deeply infiltrating endometriotic lesions in order to recognize asymptomatic ureteral strictures. In this case, intravenous or MR pyelography or a retrograde urogram allows detailed evaluation of the ureteral stenosis.

If necessary, an isotope scan should be performed to assess renal functionality.

Visible vaginal lesions should be biopsied for histological confirmation.

From Vercellini et al., Gynecol Obstet Invest 2009

Managing Rectovaginal Endometriosis

Surgical approach

The sigmoid must be gently, progressively, and amply mobilized to expose the left adnexal area.

It may be difficult to recognize the ureter, which can be dislocated superiorly and attached to the ovary, or medially and adjacent to the uterosacral ligament.

When in doubt, it may be appropriate to adopt a retroperitoneal approach to identify, dissect, and mobilize the ureter. Insertion of ureteric stents under cystoscopic control is suggested in severely altered anatomic conditions.

Different techniques have been suggested to excise deep cul-de-sac endometriotic plaques at laparotomy, laparoscopy, or by the vaginal route.

When the ureters are not involved, the major operative risk is rectal perforation.

From Vercellini et al., Gynecol Obstet Invest 2009

Managing Rectovaginal Endometriosis

Surgical approach

The upper, accessible portion of the pouch of Douglas is first freed from any ovarian endometriomas.

Bilaterally identify or dissect the ureters and develop the pararectal spaces.

Insert the index and middle fingers of the left hand into the vagina behind the cervix, pushing the posterior fornix upward.

Detach the rectum from the posterior fornix with the scissors in the right hand, directing the cuts towards the left fingertips in the vagina.

Open the fornix by cutting along the attachment of the vaginal cuff to the posterior part of the cervix.

A narrow-blade retractor is inserted between cervix and vagina, pushing the uterus towards the pubic symphysis.

Excision of the plaque and reattachment of the vagina to the cervix by means of a T-shaped suture. Reinforce the anterior rectal wall.

Managing Rectovaginal Endometriosis

Surgical approach

Rectal endometriosis can be dealt with using three different modalities: superficial thickness excision, full-thickness discoid resection/anterior rectal wall excision, and segmental colorectal resection.

Lesions < 2 cm in size or less than one third of the rectal circumference can be excised in a full-thickness manner either transabdominally or laparoscopically.

For lesions requiring segmental resection of the rectum, the proximal healthy colon should be mobilized and the ureters identified. The lower the anastomosis, the higher the probability of postoperative leakage and rectovaginal fistula formation.

The risk of leakage and fistula formation can be reduced by following the basic rules of colorectal surgery about suturing and by performing, when needed, a temporary ileostomy (from 6 weeks to 3 months).

Opening of the rectal lumen should be avoided if at all possible, because the vast majority of the severe complications of surgery for vaginal and rectal endometriosis are specifically associated with inadvertent rectal perforation or incidental resection.

Managing Rectovaginal Endometriosis

Surgical approach

Juxtaposition of full-thickness sutures of two adjacent hollow viscera with bacterial content increases the risk of fistula formation.

Optimal preoperative bowel preparation is of utmost importance.

A double-layer technique should be used, even in case of segmental rectal resection, by means of disposable stapling devices.

When reattaching the posterior vaginal wall to the cervix, sub-cuticular stitches should be adopted in order to exclude the mucosa from the suture rim.

Suction should not be applied to pelvic drains, and postoperative temporary parenteral nutrition may be taken into consideration.

The decision to resect the rectum must be shared preoperatively with the patient after providing detailed information, and should be based more on severity of symptoms than on degree of infiltration.

Managing Rectovaginal Endometriosis

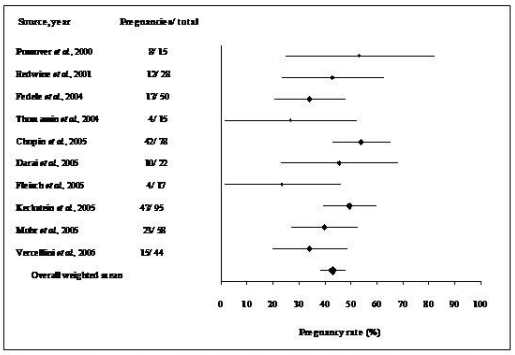
Surgical approach

When endometriotic nodules are located above the rectosigmoid junction, the sigmoid colon usually is not mobilized to the splenic flexure.

Because leakage and late functional problems are much less frequent after a sigmoid resection than after a rectum resection, an aggressive approach seems reasonable whenever sub-occlusive symptoms are present, double-contrast barium enema identifies a stricture of more than 50% of the bowel lumen, or intra-operative digital evaluation demonstrates stenosis with obstruction.

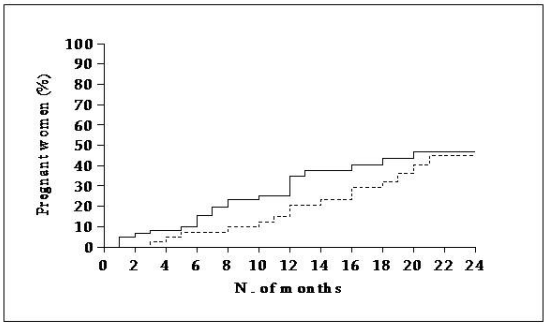
The support of an experienced colorectal surgeon and, when opportune, of a urological surgeon, increases the possibility of radical excision of deep endometriotic lesions, at the same time reducing the risk of major intra- and postoperative complications.

Pregnancy Rates Observed after Excisional Surgery of Rectovaginal Endometriosis at Laparotomy or Laparoscopy



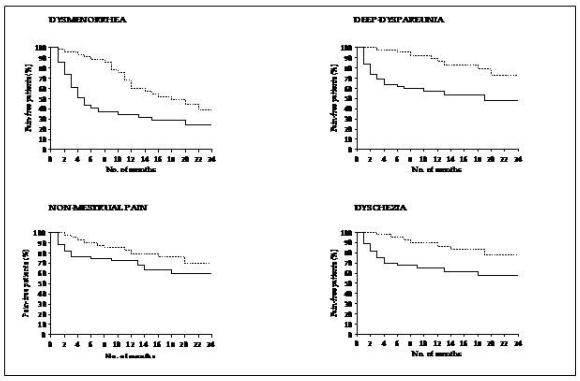
Diamonds represent percentage point estimates and *horizontal lines* 95% CIs.

From Vercellini et al., Hum Reprod 2009



Cumulative 24-month probability of becoming pregnant in 105 infertile women with rectovaginal endometriosis according to the treatment modality adopted: (- - -) radical conservative surgery at laparotomy ($n = 44$); ( ) expectant management ($n = 61$) (log rank test, $\chi^2 = .75$; $P = .38$).

Vercellini et al., Am J Obstet Gynecol 2006



24-month symptom-free survival analysis in 105 women with rectovaginal endometriosis undergoing conservative surgery at laparotomy (- - -) or expectant management ( ).

From Vercellini et al., Am J Obstet Gynecol 2006

Managing Rectovaginal Endometriosis

Effect on pain symptoms
(literature data, 2000-2008)

Substantial short-term pain relief	70-80%
Need for analgesics or hormonal treatment at 1-year	~ 50%
Medium-term recurrence of lesions	~ 20%
Need for repeat surgery	~ 25%

From Vercellini et al., Hum Reprod Update 2009

Major Intra-and Postoperative Complications of Radical Surgery for Rectovaginal Endometriosis. Literature Data, 2000-2008

Complication	Observed incidence
Neurogenic bladder dysfunction	4-10%
Rectovaginal fistula formation	2-10%
Blood transfusion	2-6%
Inadvertent rectal perforation	1-3%
Anastomotic leakage	1-2%
Pelvic abscess	1-2%
Temporary diverting loop ileostomy/colostomy	0.5-1.5%
Intraoperative ureteral lesion	0.5-1%
Postoperative ureteral fistula formation	0.5-1%
Post-anastomotic rectal stenosis	0.5-1%
Post-anastomotic ureteral stenosis	0.5-1%

From Vercellini et al., Hum Reprod 2009

Reported Incidence of Rectovaginal Fistula Formation after Radical Surgery for Deeply Infiltrating Endometriosis with Colorectal Resection

Source	Year	% with fistula
Koninckx *et al.*	1996	3.1
Camagna *et al.*	2004	6.9
Ford *et al.*	2004	1.6
Marpeau *et al.*	2004	6.3
Darai *et al.*	2005	7.5
Dubernard	2006	10.3
Landi *et al.*	2006	6.6
Mereu *et al.*	2007	2.6

From Vercellini et al., Gynecol Obstet Invest 2009

Surgery for Severe Endometriosis: Re-treatment Rate at 3- to 5-Year Follow-up

	Second-line treatment/patients	(%)
Redwine and Wright, 2001	23/67	(34)
Abbott *et al.*, 2003	44/135	(33)
Varol *et al.*, 2003	61/169	(36)
Fedele *et al.*, 2004	21/83	(25)

Norethisterone Acetate versus a Continuous Low-Dose Estroprogestin Combination in the Treatment of Rectovaginal Endometriosis

- **Objective:** to evaluate the efficacy and safety of norethisterone acetate versus a low-dose estroprogestin combination administered continuously in the treatment of pelvic pain in women with rectovaginal endometriosis not excised at previous surgery.
- **Design:** open-label, parallel-group, randomized controlled trial at a university hospital endometriosis center.

Vercellini et al., Fertil steril 2005

Norethisterone Acetate versus a Continuous Low-Dose Estroprogestin Combination in the Treatment of Rectovaginal Endometriosis

Treatments

- Oral norethisterone acetate, 5 mg/day for 1 year
- An oral estroprogestin combination containing ethinyl estradiol 0.01 mg and cyproterone acetate 3 mg given continuously for 1 year
- The subjects in the estroprogestin group who bled heavily were advised to interrupt treatment for 1 week.

Vercellini et al., Fertil Steril 2005

Pain Symptom Score in Patients with Rectovaginal Endometriosis

	Ethinyl E_2 plus cyproterone acetate group		Norethindrone acetate group	
Symptom	Visual analog scale	Verbal rating scale	Visual analog scale	Verbal rating scale
Dysmenorrhea	(n = 34)		(n = 37)	
Baseline value	72.3±16.6	2.4±0.6	75.8±18.1	2.5±0.6
12-month value	8.7±20.7	0.3±0.7	3.0±11.3	0.1±0.4
Mean decrease	63.7±23.3	2.1±0.8	72.8±22.5	2.4±0.8
Dyspareunia	(n = 23)		(n = 25)	
Baseline value	46.5±22.1	1.6±0.7	51.4±24.7	1.7±0.8
12-month value	10.8±22.9	0.4±0.8	13.8±23.0	0.5±0.8
Mean decrease	35.6±28.3	1.2±0.8	37.6±22.2	1.2±0.8
Non-menstrual pain	(n = 18)		(n = 20)	
Baseline value	52.5±23.7	1.8±0.7	57.5±24.0	1.8±0.7
12-month value	25.0±27.9	0.8±0.9	14.5±20.9	0.4±0.6
Mean decrease	27.5±31.2	0.9±0.9	43.0±21.7	1.4±0.6
Dyschezia	(n = 14)		(n = 22)	
Baseline value	52.9±15.9	1.7±0.5	53.2±22.2	1.8±0.6
12-month value	10.0±17.1	0.3±0.5	7.5±14.1	0.3±0.5
Mean decrease	42.9±22.0	1.4±0.6	45.7±21.8	1.5±0.7

Vercellini et al., Fertil Steril 2005

Norethisterone Acetate versus a Continuous Low-Dose Estroprogestin Combination in the Treatment of Rectovaginal Endometriosis

Patient satisfaction after 12 months of medical therapy according to treatment allocation

	Norethisterone acetate (n=45)		Estroprogestin combination (n=45)	
	n	(%)	n	(%)
Very satisfied	11	(24)	6	(13)
Satisfied	22	(49)	22	(49)
Uncertain	8	(18)	8	(18)
Dissatisfied	3	(7)	7	(16)
Very dissatisfied	1	(2)	2	(4)

Vercellini et al., Fertil Steril 2005

Medical Treatment of Rectovaginal Endometriosis

Side effects observed during treatment in the two study groups*

	Norethisterone acetate		Estroprogestin combination	
	n	%	n	%
Amenorrhea	29	72	17	45
Spotting	9	24	14	32
Breakthrough bleeding	2	12	7	24
Bloating/swelling	19	76	7	28
Weight gain	12†	29	7‡	17
Decreased libido	4	9	2	5
Depression	3	7	2	5
Headache	2	5	3	7
Nausea	0	-	3	7
Cutaneous eruption	1	2	-	-

*Subjects withdrawn because of side effects are included. †Mean±SD weight gain, 2.3± 1.0 kg.
‡Mean ± SD weight gain, 3.6 ± 2.3 kg

From Vercellini et al., Fertil Steril 2005

Surgery for Rectovaginal Endometriosis

The uncritical belief that medical treatments are not efficacious for rectovaginal endometriosis leads to the obvious conclusion that surgery is the only reasonable therapeutic choice.

Patients' consent to surgery should no longer be sought based solely on the purported uselessness of medical therapies.

Vercellini et al., Fertil Steril 2005

Managing Bladder Endometriosis

Bladder detrusor endometriosis, once considered rare, is now increasingly recognized.

About 1% of women with spontaneous pelvic endometriosis have urinary tract lesions, involving the bladder in 84% of the cases.

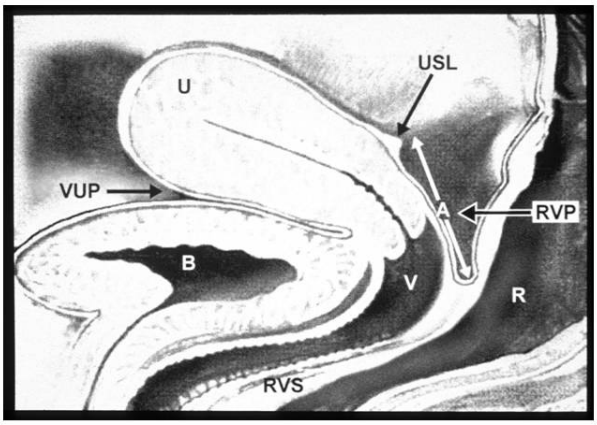
Vesical endometriosis is usually not observed in women with retroverted uterus. This is in agreement with the postulate of Jenkins *et al*. [50], as in this conditio,n no dependent anterior cul-de-sac is present.

A strong association between vesical and ureteral endometriosis has not been demonstrated.

However, bladder and ureteral endometriosis may co-exist, thus rendering the complete urological reparative procedure more complex.

Bladder Detrusor Endometriosis: Etiologic Hypotheses

1. Transtubal menstrual reflux of endometrial cells with implantation on the peritoneum covering the bladder dome
2. Metaplasia of subperitoneal müllerian remnants located in the vesicovaginal septum
3. Extension of adenomyosis from the anterior uterine wall to the bladder



From Vercellini et al., Fertil Steril 2000

The Pathogenesis of Bladder Detrusor Endometriosis

- 40 women evaluated between 1995 and 2000
- Histologically confirmed, full-thickness detrusor endometriosis
- With one exception, anterouterine pouch partially or totally obliterated
- Nodule in the posterior wall or dome of the bladder, well above the uterine isthmus, adherent to the anterior wall or fundus
- With one exception, pelvic ultrasound (US), cystoscopy, intravenous (IV) pyelography, magnetic resonance imaging (MRI), and computed tomography (CT) identified the lesion cranially with respect to the vesicovaginal septum and excluded uterine adenomyosis

From Vercellini et al., Am J Obstet Gynecol 2002

Frequency of Extravesical Endometriosis in 58 Patients with Bladder Endometriotic Nodules

Forms of disease	*n*	%	95% CI
Superficial peritoneal implants	34	59	45.2-71.2
Endometriotic ovarian cysts	26	45	32.2-58.2
Pelvic adhesions	47	81	68.4-89.6
Deep peritoneal implants	16	28	16.7-40.8
Overall	51	88	76.7-94.3

From Somigliana et al., Fertil Steril 2007

Managing Bladder Endometriosis

History

Vesical endometriosis may present with variable symptoms and insidious onset, often mimicking recurrent cystitis. Urine cultures are usually negative.

The classic clinical features are catamenial frequency, urgency and pain at micturition with vesical tenesmus of varying severity.

As endometriosis rarely infiltrates and ulcerates the mucosal layer of hollow viscera, hematuria is not frequent.

Prompt recognition of the condition is important to avoid prolonged morbidity and erroneous treatments.

Spontaneous bladder detrusor endometriosis must be distinguished from the iatrogenic form that ensues after a cesarean section.

Managing Bladder Endometriosis

Diagnosis

Ultrasonography, performed with a full bladder, identifies a heterogeneous, hyperechoic, intraluminal, usually conical vegetation, sometimes with small transonic formations, protruding from the posterior vesical wall.

A cleavage plane between the detrusor nodule and the anterior uterine wall is generally clearly detected, excluding a leiomyoma.

At median longitudinal scans, the lesions are supra-isthmic.

Vercellini et al., Gynecol Obstet Invest 2009

Managing Bladder Endometriosis

Diagnosis

Cystoscopy may demonstrate an intraluminal mass of the posterior bladder wall or dome and, in patients not operated previously, the distance between the caudal border of the endometriotic lesion and the interureteric ridge is rarely less than 2 cm.

Systematic endoscopic biopsy is critical to exclude epithelial neoplasia, as well as detrusor mesenchymal tumors. However, with the exception of transurethral resection procedures, biopsy at cystoscopy is not always diagnostic for endometriosis.

The typical bluish nodules are present in about half of the cases and the urothelium is not ulcerated. Due to the intraperitoneal origin of the lesion, cystoscopic findings may be normal.

Managing Bladder Endometriosis

Diagnosis

Intravenous pyelography classically reveals a filling defect of the bladder dome, suggesting the presence of a "high" extra-vesical lesion, and is decisive in ruling out ureteral involvement.

Intravenous pyelography should no longer be considered a standard diagnostic technique when bladder endometriosis is suspected.

MRI and CT scans confirm the ultrasonographic findings, but usually do not add different or more precise information to ultrasonography and cystoscopy, as they identify a supracervical lesion, with a cleavage plane with the anterior uterine wall.

Managing Bladder Endometriosis

Surgical approach

A wrong pathogenetic view may have major unfavorable consequences, as patients may undergo transurethral resection of endometriosis with short-term recurrence of both symptoms and detrusor disease.

The definitive solution for bladder endometriosis is transperitoneal abdominal surgery at laparoscopy or laparotomy.

Vercellini et al., Gynecol Obstet Invest 2009

Managing Bladder Endometriosis

Surgical approach

The anterior cul-de-sac is obliterated partially or totally due to extensive adhesions between the peritoneum of the bladder fold and the uterine wall and fundus. Very often one or both round ligaments are distorted and involved in the adhesive process.

The detrusor nodule is almost always identified in the posterior wall or dome of the bladder, adherent to the anterior uterine wall, generally well above the isthmus, trigone, and vesicovaginal septum. Additional pelvic endometriotic lesions are usually present.

Vercellini et al., Gynecol Obstet Invest 2009

Managing Bladder Endometriosis

Surgical approach

Careful recognition of the limits of the nodule is necessary, with lysis of any adhesions between the anterior uterine wall and the vesicouterine fold peritoneum.

An intentional perinodular incision through the vesical dome is suggested. The lesion is excised with mechanical scissors or unipolar electricity.

The bladder is finally oversewn with two transverse, watertight, fine synthetic absorbable sutures.

Recurrent lesions may infiltrate down the bladder, approaching the ureteral meatuses. In these cases, ureteral cannulation is mandatory.

Vercellini et al., Gynecol Obstet Invest 2009

Managing Bladder Endometriosis

Surgical approach

Segmental bladder resection for detrusor endometriosis is generally a relatively simple and safe procedure.

Bladder sutures heal easily due to abundant vascularization, and fistula formation is almost always prevented by sufficiently prolonged urine drainage (10 days).

Several reports demonstrated the excellent surgical outcomes of resection of bladder endometriosis in terms of symptom relief and recurrence rate, whether the procedure is carried out at laparotomy or laparoscopy.

Vercellini et al., Gynecol Obstet Invest 2009

Managing Bladder Endometriosis

Surgical approach

In case of cesarean section, one should not be tempted to schedule partial cystectomy at the same time, as the considerable increase in blood flow renders the procedure hemorrhagic.

Pregnancy status does not facilitate development of cleavage planes between the uterus and the bladder due to the firm fibrotic nature of the adhesions.

Conclusion I

Endometriosis infiltrating the posterior vaginal and anterior rectal walls usually causes severe symptoms, and the available evidence suggests that excision of deep infiltrating lesions substantially reduces both functional and organic pain.

Incomplete lesion resection generally does not achieve substantial benefits, whereas radical interventions increase the hazard of rectal and ureteral injuries with associated sequelae.

Long-term follow-up data are limited, and it is not possible to reliably predict the duration of the analgesic effect of conservative surgery.

Conclusion II

Effects on likelihood of pregnancy and time to conception in infertile women are far less clear.

Because endometriosis of the rectum and vagina is a benign condition with limited tendency to progress, the decision to undergo conservative surgery should be undertaken in selected circumstances.

The results reported after treatment of deeply infiltrating lesions are strictly operator-dependent. Complication rates are likely to increase dramatically when surgeons are not specifically trained in such particularly demanding interventions.

Conclusions III

Routine performance of urinary tract ultrasonography is strongly recommended in all women with deep endometriosis with the aim of identifying kidney damage at an early and partially reversible stage. In addition, postoperative doubts about the very cause of ureteral hydronephrosis will be prevented.

The peculiar technical problems associated with conservative surgical treatment of deep endometriotic lesions may tip the balance in favor of laparoscopy or laparotomy depending on several factors, including the need for low anterior rectal resection, ureteral stenosis with indication for ureteroneocystotomy, and the availability of a colorectal endoscopist who is expert in severe endometriosis.

Conclusions IV

Vesical endometriosis can be successfully managed at laparoscopy and, provided prolonged bladder drainage is maintained, is usually uneventful.

Considering the excellent symptomatic response to progestin or estrogen-progestogen combinations, excision of detrusor nodules is not mandatory and should be planned based on the patient's needs after clear information-gathering.

Segmental bladder resection allows spontaneous attempts at conception, avoiding frustrating vesical symptoms, but there is no demonstration that this type of lesion interferes with fertility.

Surgery for Endometriosis

Absolute Indications
- Obstructive uropathy
- Bowel stenosis
- Pelvic mass of doubtful nature

Relative Indications
- Infertility
- Pelvic pain

No Indications
- Asymptomatic lesions
- Second-look laparoscopy

The Shared Medical Decision-Making Approach

Detailed and thorough patient information is of utmost importance when choosing among therapeutic alternatives, especially:

- When dealing with benign, chronic diseases not interfering with general health.
- In cases of major differences in terms of risks and morbidity between treatment options.
- When the purported benefits of an invasive procedure are indeterminate.

Coulter A., Women & Health 2001

Surgery for Endometriosis

Obviously, the skill of the surgeon is relevant to the final outcome, but even the most talented surgeon should think before recommending surgery,
"Why do I do what I do?"

Garcia-Velasco & Arici, Fertil Steril 2004

Treatment for Endometriosis

The therapeutic approach toward patients with endometriosis should be problem-oriented and not lesion-oriented, and before suggesting systematic resection one should be reasonably confident that the chances of overcoming the main clinical problem would be substantially increased.

Vercellini et al., Hum Reprod 2009

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NOTES

RELATIONSHIP BETWEEN ENDOMETRIOSIS AND CANCER

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LEARNING OBJECTIVES;
At the conclusion of this presentation, participants should be able to:

1. Estimate the effect of endometriosis on the risk of ovarian cancer and other malignancies.
2. Describe the association of endometriosis with various ovarian cancer histologic subtypes.
3. Discuss the role of screening, medical prevention and prophylactic surgery in women with endometriosis.

Relationship Between Endometriosis and Cancer

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Relationship Between Endometriosis and Cancer

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Atypical Endometriosis

Only 6 cases out of 2000 surgical cases of endometriosis (0.003%) had cytological and histological atypia

- Müllerian seromucinous tumor, low malignant potential
  $n = 3$
- Pattern and cytologic atypia
  $n = 1$
- Mild pattern and cytologic atypia
  $n = 1$
- Mild pattern atypia
  $n = 1$

From Bedaiwy et al., Pathol Oncol Res 2009

Studies on the Frequency of Endometriosis in Patients with Ovarian Cancers According to the Malignant Histotype

Authors	Ovarian cancer histotype					Total
	Serous	Mucinous	Endometrioid	Clear cell	Other	
Aure *et al.*, 1971	0% (0/357)	1% (1/203)	9% (20/212)	24% (14/59)	...	4% (35/831)
Kurman and Craig, 1972	6% (7/118)	4% (2/47)	11% (4/37)	8% (2/28)	...	7% (15/230)
Russel, 1979	3% (7/233)	4% (3/69)	28% (20/72)	48% (16/33)	...	11% (46/407)
Vercellini *et al.*, 1993	4% (8/220)	6% (6/94)	26% (30/114)	21% (8/38)	12% (11/88)	11% (63/556)
De La Cuesta *et al.*, 1996	0% (0/10)	6% (1/18)	39% (9/23)	41% (7/17)	45% (5/11)	28% (22/79)
Toki *et al.*, 1996	10% (9/88)	9% (3/33)	30% (16/54)	50% (22/44)	0% (0/16)	21% (50/235)
Jimbo *et al.*, 1997	9% (9/92)	3% (1/35)	23% (3/13)	41% (13/32)	...	15% (25/172)
Fukunaga *et al.* 1997	10% (6/63)	6% (2/35)	42% (13/31)	54% (27/50)	67% (2/3)	27% (50/182)
Ogawa *et al.*, 2000	7% (4/60)	0% (0/17)	43% (3/7)	70% (30/43)	...	29% (37/127)
Vercellini *et al.*, 2000	3% (2/61)	3% (1/30)	20% (13/66)	14% (5/35)	6% (1/17)	10% (22/209)
Oral *et al.*, 2003	4% (3/70)	6% (2/35)	22% (4/18)	9% (1/11)	8% (4/49)	8% (14/183)

From Somigliana et al., Gynecol oncol 2006

Frequency (in Percentage) of Ovarian Cancer Cases with Endometriosis According to Histologic Subtype and Selected Characteristics, Milan, Italy, 1980 to 1990.

	Histotype					
	Serous (*n* = 220)	Mucinous (*n* = 94)	Endometrioid (*n* = 114)	Clear cell (*n* = 38)	Mixed (*n* = 36)	Other (*n* = 52)
Age (year)						
≤ 49	6.6 (5)*	16.7 (6)	34.5 (10)	29.4 (5)	16.7 (2)	13.3 (2)
≥ 50	2.5 (3)	-	27.0 (20)	14.3 (3)	25.0 (6)	2.8 (1)
Stage						
I-II	8.2 (6)	6.9 (5)	26.1 (18)	20.0 (4)	41.2 (7)	5.6 (1)
III-IV	1.4 (2)	5.3 (1)	21.6 (8)	25.0 (4)	5.6 (1)	6.6 (2)
Menopausal status						
Premenopause	4.6 (5)	11.1 (6)	23.3 (14)	23.1 (6)	20.0 (3)	8.3 (2)
Postmenopause	2.7 (3)	-	29.6 (16)	16.7 (2)	23.8 (5)	4.0 (1)
Parity						
Nulliparous	3.2 (4)†	5.8 (1)	36.0 (9)	33.3 (3)	33.3 (2)	-
Parous	2.0 (1)	6.7 (4)	20.9 (14)	22.2 (4)	18.5 (5)	10.3 (3)
Total	3.6 (8)	6.4 (6)	26.3 (30)	21.1 (8)	22.2 (8)	5.8 (3)

*The number of cases with endometriotic lesions is shown in parentheses.
†The sum does not add up to the total because of missing values.

Vercellini et al., Am J Obstet Gynecol 1993

Relationship of Endometriosis to Risk of Invasive Ovarian Cancer by Histology, Medical Condition Linked Registry Study, Denmark.

	Serous (*n* = 932)		Mucinous (*n* = 344)		Endometrioid (*n* = 300)		Clear cell (*n* = 123)	
	n	RR (95%CI)	*n*	RR (95%CI)	*n*	RR (95%CI)	*n*	RR (95%CI)
Endometriosis								
No	918	1.0	340	1.0	287	1.0	118	1.0
Yes	14	1.2 (0.7-2.0)	4	1.0 (0.3-2.7)	13	3.3 (1.9-5.9)	5	3.0 (1.2-7.4)
<1y	0	…	1	4.0 (0.5-28.6)	2	10.2 (2.5-41.0)	0	…
1-4y	4	1.4 (0.5-3.9)	2	1.9 (0.4-7.8)	4	0.4 (0.1-2.4)	1	2.6 (0.3-19.3)
≥5y	10	1.2 (0.6-2.2)	1	0.3 (0-2.6)	7	2.5 (1.2-5.4)	4	3.3 (1.2-9.1)

From Brinton et al., Cancer Epidemiol Biomarkers Prev 2005

Clinical Characteristics and Lateral Distribution of Stage I and II Epithelial Ovarian Cancer in 209 Women Studied

	Endometrioid (*n* = 66)	Serous (*n* = 61)	Clear cell (*n* = 35)	Mucinous (*n* = 30)	Mixed (*n* = 10)	Undifferentiated (*n* = 7)
Age (years)	53 (10)	53 (13)	53 (12)	51 (14)	54 (13)	49 (13)
Parous	50 [76]	47 [77]	28 [80]	22 [73]	7 [70]	5 [71]
Menopausal	31 [47]	33 [54]	17 [49]	13 [43]	5 [50]	3 [43]
Stage						
I	51 [71]	50 [82]	34 [97]	28 [93]	9 [90]	6 [86]
II	15 [23]	11 [18]	1 [3]	2 [7]	1 [10]	1 [14]
Tumor						
Left-sided	35 [53]	20 [33]	19 [54]	13 [43]	2 [20]	2 [29]
Right-sided	19 [29]	25 [41]	16 [46]	16 [53]	6 [60]	3 [43]
Bilateral	12 [18]	16 [26]	0	1 [3]	2 [20]	2 [29]
Associated endometriosis	13 [20]	2 [3]	5 [14]	1 [3]	1 [11]	0

Values are given as mean (SD) or *n* [%].

Vercellini et al., BJOG 2000

Endometriosis and Cancer

- Patients with endometriosis-associated ovarian cancer tend to be younger and diagnosed in earlier stages and with lower grade lesions.
- Overall, a better prognosis could be demonstrated in these patients.
- Multiple biases may confound the available evidence.

Somigliana et al., Gynecol Oncol, 2006

Relationship Between Endometriosis and Ovarian Cancer

Studies	Study design	Entity of the association	
		OR, SIR or RR	95% CI
Brinton *et al.*,1997	Cohort	1.9	1.3-2.8
Ness *et al.,2000*	Case-control	1.7	1.2-2.4
Ness *et al.,2002*	Case-control	1.7	1.1-2.7
Berglund *et al.*,2003	Cohort	1.4	1.2-1.7
Brinton *et al.,2003*	Cohort	1.3	0.6-2.6
Borgfeldt and Andolf, 2004	Case-control	1.3	1.0-1.7
Modugno *et al.,2004*	Case-control	1.3	1.1-1.6

OR: odds ratio, SIR: standardized incidence ratio, RR: relative risk, CI: confidence interval.

From Somigliana et al., Gynecol Oncol, 2006

Epidemiologic Cohort Studies Assessing Ovarian Cancer Risk in Endometriosis Patients

Author	Study type	Cohort size	Mean follow-up (years)	Ovarian malignancies identified	Ovarian cancer in endometriosis patients SIR/OR	
Brinton *et al.*, 1997	Cohort	20.686 endometriosis patients	11.4	29	Overall cancer risk	1.2
					Ovarian cancer	1.9
					Ovarian cancer with ≥ 10 yrs follow-up	2.5
					Ovarian cancer with long-standing endometriosis	4.2
Brinton *et al.*, 2004	Cohort	12.193 infertility patients		45	Ovarian cancer	2.5
Brinton *et al.*, 2005	Cohort			2.491	2.53 (1.19-5.38)	
Ness *et al.*, 2000	Case control			66	Ovarian cancer	1.3
Borgfeldt, Andolf, 2004	Nested case control	28.163		81	Ovarian cancer	1.3

Nezhat et al., Fertil Steril 2008

Epidemiologic Cohort Studies Assessing Ovarian Cancer Risk in Endometriosis Patients (Continued)

Author	Study type	Cohort size	Mean follow-up (years)	Ovarian malignancies identified	Ovarian cancer in endometriosis patients SIR/OR	
Modugnano *et al.*, 2004	Case control			177	1.3 (1.1-1.6)	
Melin *et al.*, 2006	Cohort	64.492	12.7	122	Overall cancer risk	1.04
					Ovarian cancer	1.43
					Ovarian cancer, early diagnosed endometriosis	2.0
					Ovarian cancer, long-standing endometriosis	2.2
Olsen *et al.*, 2002	Cohort	1.392	13	3	No increased risk for overall or ovarian cancer	
Kobayashi *et al.*, 2007	Cohort	6.398	12.8	46	Ovarian cancer	8.95
					Ovarian cancer > 50 years old	13.2

Nezhat et al., Fertil Steril 2008

Observed Numbers of Ovarian Cancers, Standardized Incidence Ratios (SIR), and 95% CI for the 6,398 Assessable-Case Patients with Ovarian Endometrioma by Years of Follow-up and Age at Ovarian Endometrioma Diagnosis

Variable	Observed	SIR	95% CI
Ovarian cancer	46	8.95	4.12-15.3
Years of follow-up, Years			
< 8	9	19.3	6.94-30.6
8-12	12	6.42	4.79-8.01
>13	25	8.92	4.79-8.01
P value for trend		0.021	
Age at diagnosis, year			
20-29	2	3.88	1.28-4.61
30-39	5	4.85	2.09-7.74
40-49	13	8.03	4.78-11.9
50-59	26	13.2	8.87-18.5
P value for trend		0.014	

Modified from Kobayashi et al., Int J Gunecol Oncol 2007

Austin Bradford Hill Criteria

Criteria	Comment
Strength of the association	If the relative risk is "strong", there is less likelihood that there are other adequate explanation for the observed association.
Consistency	Is the association consistent over the various studies?
Biological gradient	Is there an exposure-response relationship exhibited over the range of studies?
Specificity	Is the association limited to a particular outcome?
Temporality	Does the exposure precede the outcome?
Biological plausibility	Is the proposed association explained by a biologically plausible mechanism?
Experimental evidence	Are there experimental studies that support the association?
Analogy	Is the proposed causal relationship analogous to some other accepted cause and effect?
Coherence	Does the proposed relationship seriously conflict with generally known facts about the natural history and biology of the disease?

From Viganò et al., Fertil Steril, 2007

Does Endometriosis Really Have Premalignant Potential?

- Only 15% of patients harbor monoclonal lesions.
- Development of any kind of cancer was not associated with the finding of monoclonal cell populations.
- There is still no evidence to classify endometriosis as a premalignant condition.
- Endometriosis appears as a completely benign disease with no direct relationship to gynecological cancer of any kind.

Mayr et al., The FASEB Journal, 2003

Endometriosis and Cancer

- Endometriosis does not appear to be associated with an increased risk of cancer in general.
- Data from large case-control and cohort studies suggest an association between endometriosis and ovarian cancer, with an observed increase in risk between 30 and 90%.
- Most of the observed-effect sizes are modest.
- The demonstration of an association cannot be used to infer causality.

Somigliana et al., Gynecol Oncol 2006

Endometriosis and Cancer

Lifetime risk of:

- Endometrial carcinoma 2%
- Ovarian carcinoma 1%
- Malignant degeneration of endometriosis 1%
- Breast cancer 5%

Endometriosis and Cancer

- Whether or not endometriosis should be considered a preneoplastic disease represents a major and controversial issue.
- Similarly to its eutopic counterpart, studies on the epithelial lining of cystic ovarian endometriosis have documented the presence of metaplastic, hyperplastic or atypical changes.
- Carcinoma may arise from endometriosis through a multistep phenomenon, where typical endometriosis may change into severe atypia with or without hyperplasia.

Somigliana et al., Gynecol Oncol, 2006

Endometriosis and Cancer

- The likelihood of malignant degeneration of eutopic and ectopic endometrium appears similar.
- The clinical impact differs due to the site of cancer development (intrauterine versus intraperitoneal).

Endometriosis and Cancer

- "The correlation of endometriosis and malignancy may require earlier and more meticulous surgical intervention for complete disease treatment."
- "With the correlation of endometriosis and ovarian cancer continuing to strengthen over time, appropriate and timely resection and elimination of disease should be practiced."

Nezhat et al., Fertil Steril 2008

Endometriosis and Cancer

Does the observed increase in risk of ovarian cancer associated with endometriosis justify,

1. Prophylactic surgery?

and

2. Screening for asymptomatic disease?

Risk of Epithelian Ovarian Cancer in Relation to Endometriosis Diagnosis and Ovarian Surgery.

	Controls	Borderline tumors		Invasive tumors		All tumors
	(n = 1313)[a]	Cases (n = 215)[a]	OR[b] (95% CI)	Cases (n = 591)[a]	OR[b] (95% CI)	Cases (n = 806)[a]
Ever diagnosed with endometriosis[c]						
No	1.199	195	1.0	521	1.0	716
Yes	94	17	0.9 (0.5-1.6)	64	1.5 (1.1-2.1)	81
Ovarian surgery after endometriosis[c]						
No	73	12	0.8 (0.4-1.6)	53	1.6 (1.1-2.3)	65
Yes	20	4	0.9 (0.3-2.8)	10	1.2 (0.5-2.5)	14
Had ovarian surgery at least five years before diagnosis/reference date						
	16	4	1.2 (0.4-3.8)	9	1.3 (0.6-3.0)	13

[a]Numbers in column may not sum to total due to missing values. [b]Adjusted for age, calendar year of diagnosis/reference date, county of residence, number of full term births, and duration of hormonal contraception. [c]For relevant analyses, excludes women with cysts or endometriosis diagnosed within the year before reference, as well as those whose ovarian surgery occurred within the year before the reference date.

From Rossing et al., Cancer Causes Control 2008

Risk of Invasive Epithelial Ovarian Cancer in Relation to Endometriosis Diagnosis and Ovarian Surgery by Histologic Type of Tumor

	Controls	Serous invasive tumors		Endometrioid and clear cell invasive tumors		Other invasive, excluding mucinous	
	(n = 1313)[a]	Cases (n = 332)[a]	OR[b] (95% CI)	Cases (n = 133)[a]	OR[b] (95% CI)	Cases (n = 103)[a]	OR[b] (95% CI)
Ever diagnosed with endometriosis[c]							
No	1.199	298	1.0	105	1.0	96	1.0
Yes	94	31	1.3 (0.9-2.1)	26	2.8 (1.7-4.7)	7	0.9 (0.4-2.0)
Ovarian surgery after endometriosis[c]							
No	73	24	1.3 (0.8-2.2)	23	3.2 (1.9-5.6)	6	0.9 (0.4-2.3)
Yes	20	6	1.3 (0.5-3.2)	3	1.6 (0.4-5.7)	1	0.7 (0.1-5.1)
Had ovarian surgery at least five years before diagnosis/reference date							
	16	6	1.5 (0.6-3.9)	2	1.5 (0.3-6.7)	1	0.8 (0.1-6.5)

a]Numbers in column may not sum to total due to missing values. bAdjusted for age, calendar year of diagnosis/reference date, county of residence, number of full term births, and duration of hormonal contraception. cFor relevant analyses, excludes women with cysts or endometriosis diagnosed within the year before reference, as well as those whose ovarian surgery occurred within the year before the reference date.

From Rossing et al., Cancer Causes Control 2008

Endometriosis and Cancer

- The vast majority of epidemiologic studies conducted to evaluate the association between endometriosis and cancer are based on patients who had undergone surgery for diagnosis and treatment.
- Therefore, it is unclear whether conservative surgery might constitute a protective factor toward future risk of ovarian cancer development.

Endometriosis and Cancer
Diagnosis of Endometriosis

- "Proteomic profiling in combination with bioinformatics software has the potential for major diagnostic contributions for the endometriosis disease process."
- "These updated techniques may have a complementary role in diagnosing patients with endometriosis, and thus a population with an increased cancer risk."

Nezhat et al., Fertil Steril 2008

Endometriosis and Cancer

SCREENING is defined as a procedure to help identify, in an organized way, a specific disease or condition among asymptomatic individuals.

A DIAGNOSTIC TEST is defined as the application of a variety of examinations or tests to patients who have actively sought health care services to identify the exact cause for their complaints.

Sackett and Holland, 1975

Endometriosis and Cancer

DIAGNOSTIC TESTS are also applied to individuals who seek medical care because of positive or suspicious findings resulting from a screening test.

DIAGNOSTIC TESTS should be highly accurate.

SCREENING TESTS should be relatively simple and quick to perform.

SCREENING TESTS are allowed to possess higher error rates, and thus may be less accurate than diagnostic tests.

Wilson and Jungner, 1968

Endometriosis and Cancer

Characteristics of an Optimal Screening Test

- The condition sought should have significant risk of morbidity and mortality.
- Diagnosing the disease before symptoms occur results in better outcomes than waiting for symptoms.
- A useful follow-up test is available to determine which individuals with a positive screening test require treatment.
- Consensus exists regarding proper management of abnormal test results.
- The risk of complications from the test and subsequent evaluation and treatment is lower than the risk of morbidity from the disease.
- The test is accurate and reliable.
- The cost of testing and treating asymptomatic disease is acceptable.

Sackett and Holland, 1975

Endometriosis and Cancer

Characteristics of an Optimal Screening Test

- Knowledge of the natural history of the target condition is clearly important for the assessment of the results of early treatment.
- Highly sensitive tests are needed when there is an important penalty for missing the disorder.
- In screening programs, false-positive test results produce most of the problems because healthy individuals are subjected to often expensive, time-consuming and potentially dangerous diagnostic procedures that would not be experienced without the screening test.

Peters et al., 2006

Prerequisites for a Successful Screening Program

- Clear targets
- Condition amenable to treatment or prevention
- Safe and acceptable test
- Adequate infrastructure
- The severity and/or frequency of the target condition should be sufficient to justify the cost of screening.

Targeted Screening Program

Systematic testing of a selected group considered be at increased risk (e.g., first-degree relatives of women with endometriosis)

Peters et al., 2006

Endometriosis and Cancer: The Worst Scenario

- Relative risk (RR) of ovarian cancer = 2
- Lifetime probability of developing ovarian cancer = 2/100 (general female population = 1/100)
- 100% risk increase
- 98% instead of 99% chance of NOT developing ovarian malignancy
- Infertile subjects, RR = 2 (primary infertility, RR = 2.7)
- Women with an affected first-degree relative, RR = 2 (except BRCA 1 and 2 subgroups)
- Lifetime probability of developing breast cancer = 1/20

Vercellini et al., Fertil Steril 2009

Time to Stop Ovarian Cancer Screening in BRCA1/2 Mutation Carriers?

"Annual gynecological screening of women with a BRCA 1/2 mutation to prevent advanced stage ovarian cancer is not effective."

Van De Velde et al., Int J Cancer 2009

Oral Contraceptive (OC) Use and Ovarian Cancer Risk in Women with Endometriosis

Women with endometriosis are at increased risk of ovarian cancer.
(OR, 1.32; 95% CI, 1.06-1.65)

OC use for > 10 years is associated with a substantial reduction in risk among women with endometriosis.
(OR, 0.21; 95% CI, 0.08-0.58)

From Modugno et al., Am J Obstet Gynecol 2004

Distribution and Adjusted Odds Ratios (95% CI) for the Association Between Reproductive and Hormonal Factors and Risk of Endometrioid and Clear Cell Ovarian Cancers

	Controls *n* (%)	Endometrioid *n* (%)	Endometrioid OR[a] (95% CI)	Clear cell *n* (%)	Clear cell OR[a] (95% CI)
Number of pregnancies					
Nulliparous	180 (12)	33 (23)	1.0	31 (34)	1.0
1-2	645 (43)	55 (39)	0.5 (0.3-0.8)	35 (39)	0.2 (0.1-0.4)
> 3	683 (45)	54 (38)	0.4 (0.2-0.7)	24 (27)	0.1 (0.07-0.2)
			P for trend 0.001		*P* for trend< 0.0001
Hormone contraceptive use					
Never	325 (22)	50 (35)	1.0	35 (39)	1.0
< 5 years	365 (24)	42 (30)	0.7 (0.4-1.1)	26 (29)	0.9 (0.5-1.5)
≥ 5 years	813 (54)	49 (35)	0.3 (0.2-0.5)	28 (32)	0.4 (0.2-0.6)
			P for trend < 0.0001		*P* for trend 0.0002
Endometriosis (ever)[b]	87 (6)	18 (13)	2.2 (1.2-3.9)	13 (15)	3.0 (1.5-5.9)

[a] Adjusted for age, education, parity and hormone contraceptive use.
[b] Additionally adjusted for BMI.

Modified from Nagle et al., Eur J Cancer 2008

Endometriosis, OCs, and Ovarian Cancer

"To date, only OCs have emerged as chemopreventive agents against ovarian cancer. OCs are prescribed commonly for women with endometriosis. Our data suggest that this clinical practice may have an added benefit: protection against ovarian cancer. When women with endometriosis are being treated, the use of OCs, especially long-term use, should be encouraged."

From Modugno et al., Am J Obstet Gynecol 2004

Hormone Replacement Therapy (HRT) in Women with a Past Medical History of Endometriosis

- Eutopic and ectopic endometrium share similar risk factors for malignant degeneration.
- Unopposed estrogens have been observed to increase the risk of developing cancer in endometriotic implants.
- The use of combined preparations is strongly suggested, even after hysterectomy.

Salman and Hillard, Climateric 2006
Haney and Wild, Menopause 2007
Oxholm et a., Acta Obstet Gynecol Scand 2007

Endometriosis and Non-genital Cancer

- The potential association between endometriosis and breast cancer remains unclear.
- The risk of cervical cancer is reduced in patients with endometriosis.
- No association has been found between endometriosis and endometrial carcinoma.
- An association between endometriosis and melanoma has been reported.
- Large, population-based cohort studies have independently documented an association between endometriosis and non-Hodgkin's lymphoma.

Relationship Between Endometriosis and Non-ovarian Gynecological Cancers

Studies	Study design	Entity of the association	
Breast cancer		OR, SIR or RR	95% CI
Moseson *et al.*, 1993	Case-control	4.3	0.9-20.4
Schairer *et al.* (A), 1997	Cohort	3.2	1.2-8.0
Schairer *et al.* (B), 1997	Cohort	3.0	0.7-4.1
Brinton *et al.*, 1997	Cohort	1.3	1.1-1.4
Weiss *et al.*, 1999	Case-control	1.1	0.7-1.8
Venn *et al.*, 1999	Cohort	1.0	0.7-1.5
Olson *et al.*, 2002	Cohort	1.0	0.8-1.2
Borgfeldt and Andolf, 2004	Case-control	1.1	1.0-1.2
Brinton *et al.*, 2005	Cohort	0.8	0.6-1.1

OR: odds ratio, SIR: standardized incidence ratio, RR: relative risk, CI: confidence interval.
The study from Schairer et al. focuses on two different cohorts:patients who underwent hysterectomy (A) and those who underwent oophorectomy (B).

From Somigliana et al., Gynecol Oncol, 2006

Relationship Between Endometriosis and Non-ovarian Gynecological Cancers *(Continued)*

Studies	Study design	Entity of the association	
Cervical cancer		OR, SIR or RR	95% CI
Brinton *et al.*, 1997	Cohort	0.7	0.4-1.3
Berglund *et al.*, 2003	Cohort	0.6	0.5-0.8
Borgfeld and Andolf, 2004	Case-control	0.6	0.4-0.9
Endometrial cancer			
Brinton *et al.*, 1997	Cohort	1.1	0.6-1.9
Olson et al., 2002	Cohort	1.2	0.6-2.5
Borgfeld and Andolf, 2004	Case-control	0.6	0.4-0.8
Brinton et al., 2005	Cohort	0.8	0.3-1.9

From Somigliana et al., Gynecol Oncol, 2006

Relationship Between Endometriosis and Non-ovarian Gynecological Cancers *(Continued)*

Studies	Study design	Entity of the association	
Melanoma		OR, SIR or RR	95% CI
Wyshak *et al*, 1989	Case-control	3.9	1.2-12.4
Frisch *et al.*, 1992	Case-control	1.1	0.5-2.3
Holly *et al.*, 1995	Case-control	0.9	0.5-1.4
Brinton *et al.*, 1997	Cohort	1.0	0.7-1.5
Olson *et al.*, 2002	Cohort	0.7	0.2-1.8
Brinton *et al.*, 2005	Cohort	2.1	1.0-4.4
Non-Hodgkin's lymphoma			
Brinton *et al.*, 1997	Cohort	1.8	1.2-2.6
Olson *et al.*, 2002	Cohort	1.7	1.0-2.9
Berglund *et al.*, 2003	Cohort	1.2	1.0-1.5

From Somigliana et al., Gynecol Oncol, 2006

Rate Ratios of Selected Cancer Sites among Infertile Women with Endometriosis

Type of cancer	RR	95% CI
Colon ($n = 28$)	2.0	0.7-5.4
Breast ($n = 292$)	0.8	0.6-1.1
Uterus ($n = 39$)	0.8	0.3-1.9
Ovary ($n = 45$)	1.3	0.6-2.6
Melanoma ($n = 42$)	2.1	1.0-4.4
Thyroid ($n = 18$)	3.1	0.9-10.7

From Brinton et al., Epidemiology 2005

Endometriosis and Cancer Conclusions I

- Women with endometriosis are at double the risk for ovarian cancer.
- Endometriosis is associated with a 4- to 5-fold increase in risk of endometrioid and clear-cell ovarian carcinomas.
- Conceivably, most endometrioid and clear-cell ovarian carcinomas derive from endometriosis.

Endometriosis and Cancer Conclusions II

- It may not be excluded that ectopic endometrium undergoes malignant transformation with a frequency similar to its eutopic counterpart.
- Endometriosis does not seem to represent a *premalignant condition,* which is generally defined as the disordered growth characterized by changes in size, shape or differentiation of cells accompanied by specific genetic mutations predisposing a patient to the development of carcinomas.

Endometriosis and Cancer Conclusions III

- OC use is associated with 80% reduction in risk of ovarian cancer in women with endometriosis who use the drug for > 10 years.
- Prescription of OCs for long periods of time seems wise in women with recurrent endometriosis.
- Combined HRT is indicated in women with a past history of endometriosis, even after definitive surgery.

Endometriosis and Cancer
Conclusions IV

There is insufficient scientific evidence to definitively conclude that:

1. Endometriosis is a preneoplastic condition

2. Screening of asymptomatic subjects is warranted

3. Prophylactic surgery is opportune.

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NOTES

THE ROLE OF ROBOT-ASSISTED LAPAROSCOPY IN RADICAL ENDOMETRIOSIS SURGERY

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LEARNING OBJECTIVES:
At the conclusion of this presentation, participants should be able to:

1. Discuss the rationale for the use of robot-assisted laparoscopy.
2. Describe the advantages and disadvantages of utilizing a robotic system.
3. Demonstrate the application of robotic technology via case scenarios.

The Role of Robot-Assisted Laparoscopy in Radical Endometriosis Surgery

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ASRM 2009

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At the conclusion of this presentation, participants should be able to:

- Discuss the rationale for the use of robot-assisted laparoscopy.
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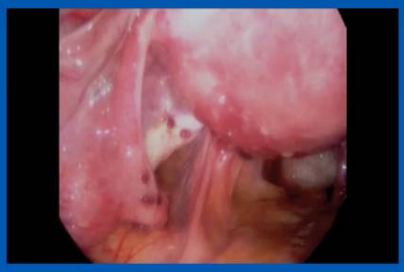
Disclosure

Intuitive Surgical, Inc. - Proctor

Locations of Endometriosis



Posterior cul-de-sac

Ovaries

Ovarian fossa

Anterior cul-de-sac

Bowel/appendix

Goals of Conservative Surgery

- Excision or ablation of endometrial implants
- Resection of endometriomas (including the cyst wall)
- Adhesiolysis
- Restoration of normal anatomy

Extirpative Surgery

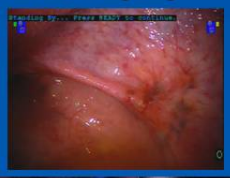
- Salpingectomy or oophorectomy
- Removal of rectovaginal or bladder disease
- Hysterectomy
- Appendectomy

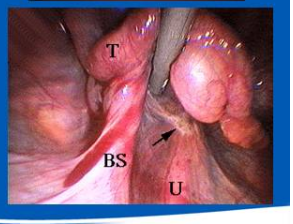
Components of Appropriate Treatment

- Accurate diagnosis
- Surgical skills : knowledge of anatomy, knowledge of energy, advanced endoscopic skills (suturing, ureterolysis, adhesiolysis, etc.)
- Multidisciplinary team : gynecologist, bowel surgeon, urologist, pain specialist

Basic Principles to Avoid Injury

- Use minimal cautery
  - Use monopolar with caution
- Bladder delineation
  - Retrograde fill the bladder
  - Cystoscopy
- Identify the ureter
  - Trace ureter to the pelvic brim
  - Look for peristalsis
- Outline the rectosigmoid
  - EEA sizer in the rectum
  - Check for injury by insufflating rectum with air while occluding sigmoid





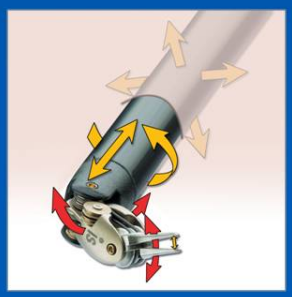
Conventional Laparoscopy Challenges

- Limited degree of motion within the body
- Hand movement is counter-intuitive (fulcrum effect)
- View of operative field is on a 2-D monitor
- Unsteady image
- Significant learning curve exists for advanced cases

da Vinci® Surgical System

Robotic Highlights

- Surgeon controls the robotic arms remotely
- 3-D image through stereoscopic viewer
- No haptic (tactile) feedback
- 7 degrees of movement mimic human wrist movement (eliminate fulcrum effect)
- Tremor filtration and motion scaling



System Upgrades

- da Vinci® S Surgical System
- High definition (HD) option
- Telestration
- Tile Pro

Significant Robotic Regulatory Milestones

- April 2005: FDA Clears *da Vinci*® System for gynecologic procedures
- May 2001: FDA Clears *da Vinci*® System for radical prostatectomy
- March 2001: FDA Clears *da Vinci*® System for general non-cardiovascular thoracoscopic surgery
- July 2000: FDA Clears *da Vinci*® System for laparoscopic surgery
- July 1997: FDA Clears *da Vinci*® System for surgical assistance

Intuitive Surgical Overview

Philosophy

- Robotics may allow for conversion of cases done by laparotomy to laparoscopy
- Robotics can be looked upon as enabling technology:
  - Shorten learning curves for advanced laparoscopic procedures
  - Level playing field between novice and expert

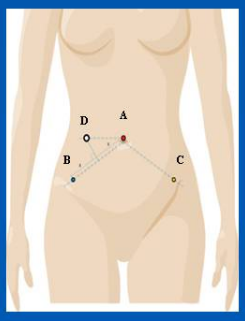
Sarle R, et al. 2004

Endowrist® Instrumentation

Courtesy of Intuitive Surgical

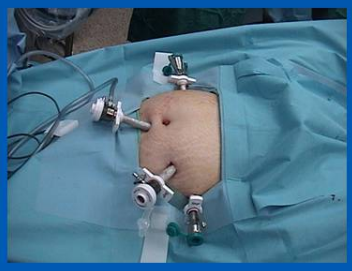
Port Placement

- A: 12 mm camera
- B: 8 mm right lower quadrant
- C: 8 mm left lower quadrant
- D: 10-12 mm accessory port, this can be placed on either the right or left side



Port Placement

- For larger uteri, consider higher port placement



Early Feasibility Studies

	Diaz-Arrastia	Beste	Advincula	Marchal	Koh (2007)
Type of hysterectomy	IIB (10) Staging (1)	IVE	IVE (5) III (1)	IIB (23) IVE (6)	IVE
Study subjects	11	11	6	30	91
Age	55y	38y	40y	53y	50y
BMI (kg/m^2)		26	26		27.9
Indications for surgery	Recurrent CIN 3, pelvic mass, endometrial CA, postmenopausal bleeding, ovarian CA	Menorrhagia, dysmenorrhea, pelvic pain, symptomatic fibroids	Endometriosis, abnormal uterine bleeding, symptomatic fibroids	Endometrial CA, Cervical CA, Benign pathologies	Menorrhagia, dysmenorrhea, pelvic pain, ovarian neoplasms
EBL	300mL (50-1500)	25-350mL	87.5mL (50-150)	83mL (0-900)	78.6mL
Blood transfusion	1	0	0		0
Uterine wt.		49g-227g	121.7g		135.5g
Operating time	270-600min	148-277min	254min(170-368)	185min (43-315)	128min
Hospital stay	2days	1day	1.3days	8days	1.35days
Complications	Conversion to minilaparotomy (1)	Conversion to open case (1) Cystotomy (1)	Vaginal cuff hematoma (1)	Venous Phlebitis(1) Lymph collection(1) Pelvic hematoma(1) UTI (1) Vaginal Hemorrhage (1)	Enterotomy(1) Vagina cuff abscess (1) Pneumonia(1) Ileus (1) Colitis (1)

Use of Robotics for Endometriosis: Feasibility

- Asymptomatic rectal and bladder endometriosis[1]
  - 23-year-old woman with 4 cm bladder mass and rectal nodule
  - Cystoscopic directed biopsies demonstrated endometriosis
  - Robot-assisted laparoscopic partial cystectomy and excision of rectal nodules
  - No postoperative complications
- Severe pelvic and infiltrative bladder endometriosis[2]
  - 32-year-old woman with dysmenorrhea, dyspareunia, hematuria, dysuria
  - Magnetic resonance imaging (MRI) with soft tissue mass along posterior bladder
  - Robot-assisted laparoscopic partial cystectomy and excision of endometriosis lesions
  - Symptoms resolved and spontaneous conception 2 months after surgery

Chammas MF et al. 2008[1], Liu C et al. 2008[2]

Case 1

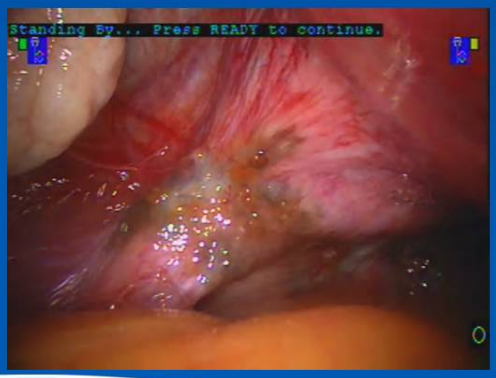
- 27-year-old G_0 patient with symptomatic advanced endometriosis
  - Dysmenorrhea
  - Dyschezia
  - Deep dyspareunia
- Previous laparoscopy demonstrated extensive endometriosis of the uterosacral ligaments and a partially obliterated cul-de-sac, which were not treated at the time of surgery.

Endometriosis Implants and Deep Infiltrating Disease

- **Implants**
  - **Treating the implants does improve pain at 6 months.[1]**
    - » **Excision of implants**
    - » **80% improvement at 6 months compared to no treatment**
  - **Excision vs. ablation[2]**
    - » **Randomized clinical trial (RCT) (n = 24)**
    - » **Equally effective, but the study did not include deeply infiltrating disease**

Abbott et al. 2004[1], Wright et al. 2005[2]

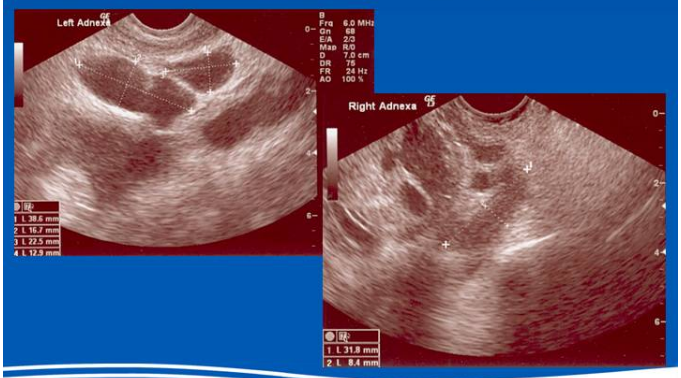
Excision of Endometriosis



Case 2

- 32-year-old G0 patient with primary infertility and known history of stage IV endometriosis
  - Previous laparotomy for bilateral endometriomas (6 cm)
  - Frozen pelvis
- Strong desire for future fertility – normal infertility work-up other than endometriosis
  - Plan for IVF → fluid noted in the endometrial canal at the time of potential embryo transfer.

Transvaginal Sonography

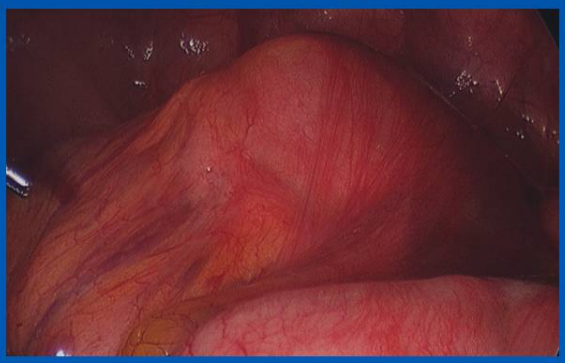


Impact of Hydrosalpinges on ART

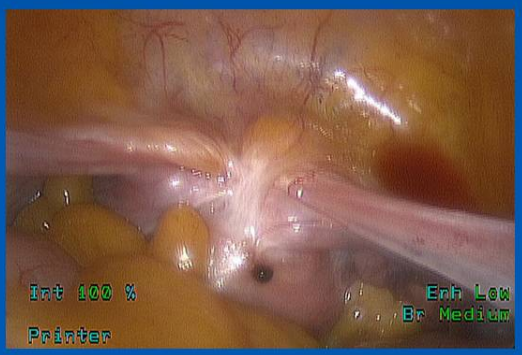
- Clinical pregnancy rate with hydrosalpinx is 30-50% less than in patients with no hydrosalpinx.
- Hydrosalpinx also leads to a two-fold increase in miscarriage rates.
- Removal of a hydrosalpinx (unilateral or bilateral) significantly improves IVF outcomes.

Camus et al. 2001, Johnson et al. 2004, Barmat et al. 1999, Strandell et al. 2007

Stage IV Endometriosis with Bilateral Hydrosalpinges



Bladder Endometriosis



Case 3

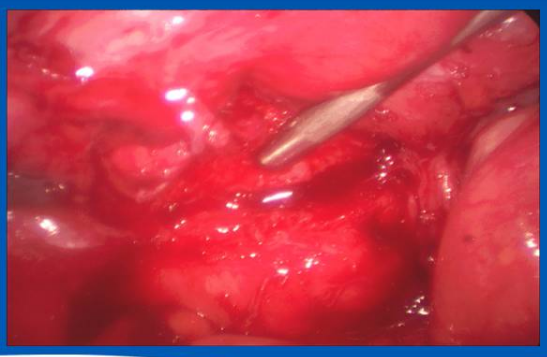
- 44-year-old G_6P_3 patient with pelvic pain and endometriosis who had previously undergone:
  - Supracervical hysterectomy/right salpingo-oophorectomy
  - Trachelectomy/left salpingo-oophorectomy
- Re-presented with recurrent pelvic pain and postcoital vaginal bleeding
- Examination revealed nodularity in the recto-vaginal septum

Rectovaginal Disease

- Limited disease progression
- Relatively high-morbidity surgery
  - Complications are usually due to bowel perforation
    - » may include abscess formation, urinary retention, constipation, ostomy, rectovaginal fistula
- Careful and thorough discussion of risks and benefits is crucial prior to surgical intervention.

Fedele et al. 2004, Vercellini et al. 2009

Rectovaginal Nodule



Case 4

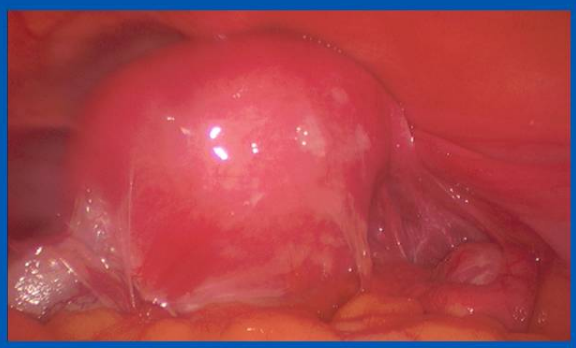
- 37-year-old G0 patient with a long history of endometriosis
  - + dysmenorrhea, dyschezia, non-cyclic pelvic pain
  - Prior treatment with oral contraceptive pills, GnRH-agonists, NSAIDs
  - 6 previous surgeries for endometriosis (laparoscopy and laparotomy)
- Examination revealed a retroverted uterus - fixed on the left side + visible nodule in the left vaginal fornix; 3 cm palpable nodule on rectovaginal exam
- MRI showed a 2 cm lesion to the left of the cervix in the posterior vagina
- She desired definitive therapy .

GnRH = gonadotropin-releasing hormone
NSAIDs= non-steroidal anti-inflammatory drugs

Indications for Hysterectomy in Women with Endometriosis

- Chronic pelvic pain with significant reduction in quality of life
- Unresponsive to medical therapy and prior conservative surgical therapy
- No desire for future fertility
- If undergoing oophorectomy, understands and accepts the impact on other health parameters
  - Osteoporosis, cardiovascular disease, sexual dysfunction, menopausal symptoms, long-term risks/benefits of hormone replacement therapy, etc.

Hysterectomy



Hysterectomy Is Not Definitive for ALL Endometriosis or Chronic Pelvic Pain

	Recurrent pain	Reoperation for recurrent pain
Namnoun 1995		
Hysterectomy	62%	31%
Hysterectomy +BSO	10%	3.7%
Matorras 2002		
Hysterectomy +BSO	0%	
Hysterectomy +BSO +HRT	2.5%	3.7%

BSO = bilateral salpingo-oophorectomy
HRT = hormone replacement therapy

Namnoun et al. 1995; Matorras et al. 2002

Reoperation-Free Survival Estimates

	2 years	5 years	7 years
Laparoscopy	79%	51%	41%
Hysterectomy	93%	85%	78%
Hysterectomy + oophorectomy	96%	92%	92%

- In women <40 years old, removal of the ovaries did not significantly improve the surgery-free time.

Shakiba et al. 2008

Hysterectomy for "Endometriosis"

- Treat other possible sources of pain
  - Irritable bowel syndrome
  - Interstitial cystitis/ painful bladder syndrome
  - Myofascial pain syndrome
    - Levator ani syndrome (tension myalgia of the pelvic floor)
    - Pyriformis syndrome
    - Coccydynia
  - Fibromyalgia

Limitations

- Bulky design
  - Limited vaginal access
- Lack of tactile feedback
  - Bedside assistant
- Solo surgeon
  - Impact on residency training
- Cost

Robotic vs. Abdominal Myomectomy: Costs

	Laparotomy (N=29)		Robotic (N=29)		P value
Charges	**Mean**	**Std Dev**	**Mean**	**Std Dev**	
Professional	4664.48	642.11	5946.48	1447.17	0.0002
Hospital	13400.62	7747.26	30084.20	6689.29	<0.0001
Total (professional + hospital)	18065.10	8005.63	36030.67	6945.50	<0.0001
Charges and Reimbursements ($)					
Reimbursements					
Professional	1841.99	827.51	2263.02	1354.97	0.2831
Hospital	7015.24	3467.97	13181.39	10752.00	0.0372
Total (professional + hospital)	8857.24	3771.26	15444.41	11638.83	0.0205

Advincula et al. 2007

Robotic vs. Abdominal Myomectomy: Costs

	Laparotomy (N=29)		Robotic (N=29)		P value
	Mean	**Std Dev**	**Mean**	**Std Dev**	
Operating room	2165.25	429.39	16915.84	2667.79	<0.0001
Anesthesia	364.46	69.21	445.48	109.42	0.0005
Nursing	2371.05	1714.50	1332.36	1057.42	<0.0001
Laboratory	139.10	147.54	113.95	92.32	0.1663
Pharmacy	322.24	298.50	255.58	183.64	0.2078
Recovery room	474.04	181.54	444.88	100.61	0.9380

Advincula et al. 2007

Costs

- Tubal re-anastamosis[1]
  - Hospital cost
    - » Robotic: $13,773.55 vs. open: $11,742.97
  - Cost per delivery
    - » Robotic: $92,488 vs. open: $92,205.90
- Endometrial cancer staging[2]
  - Laparotomy:$12,943.60
  - Laparoscopy: $7569.80
  - Robotics: $8212.00

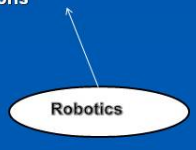
Dharia Patel et al. 2008[1], Bell et al. 2008[2]

Future Directions

- Prospective comparative studies
- Directed cost analyses
- Training programs for residency programs

Centers for Endometriosis

- Gynecologists and infertility specialists
- Multidisciplinary surgical team with a surgically experienced gynecologist working together for complex cases with urologists and general surgeons
- Pain specialists
- Nurses
- Physical therapists
- Counselors
- Psychologists/psychiatrists
- Nutritionists/dieticians
- Patient support organizations



D'Hooghe et al. 2006

Summary

- Robotics is not for every procedure or surgeon
  - **Enhance complex ,minimally invasive gynecologic procedures**
  - **Enabling technology**
  - **Increase minimally invasive surgical options (a laparotomy becomes a laparoscopy)**
- Technical and procedural limitations
  - **Lack of tactile feedback**
- Costs $$$

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NOTES

NOTES

Course #4 Test Questions

1. A 20-year-old woman presents with increasing dysmenorrhea and deep dyspareunia. She has a history of neonatal necrotizing enterocolitis, which required a colectomy. You feel that laparoscopy for diagnosis of possible endometriosis is contraindicated. You would like your pathologist to examine an endometrial biopsy for the presence of neural tissue. Which one of the following would you ask the pathologist to look for in the specimen?

    a. The presence of myelinated nerve fibers
    b. Specific immunohistochemical staining for the protein gene product 9.5.
    c. The intense expression of nerve growth factor in the endometrial stroma
    d. Nerve fibers expressing the two main immunohistochemical markers identifying sensory nerve fibers (substance P and calcitonin gene-related peptide)
    e. Small nerve trunks detected with standard histology staining

2. Which one of the following is the most effective route of progestogen delivery for preventing new endometriosis from developing following laparoscopic excision?

    a. Intrauterine
    b. Intramuscular
    c. Oral
    d. Subdermal
    e. Transdermal

3. A 38-year-old woman who had an operative laparoscopy for stage II endometriosis 5 years ago presents with pelvic pain. Which one of the following can you tell her to expect?

    a. After another surgery, there is an 80% chance she will have recurrence of pain within 3 years.
    b. Six months of medical therapy will lead to pain relief for another 5 years.
    c. There is an approximately 50% chance her ASRM disease scoring will be the same 6 months from now.
    d. The recurrence is surprising, given that surgery leads to a <20% recurrence rate 5 years later.
    e. There is an approximately 30% chance her ASRM disease scoring will be worse 6 months from now.

4. A 32-year-old woman had a 3.5-cm endometrioma resected from her ovary and is now interested in IVF. Which one of the following statements is true?

    a. The ovary that had the surgery will tend to respond similarly to the contralateral ovary.
    b. Excision, rather than cauterization, of the cyst gives her a better chance at achieving pregnancy.
    c. The ovulation rate in the postoperative ovary will not be significantly diminished.
    d. Her IVF success rate is no different than that of a woman with tubal factor undergoing IVF.
    e. The preferred surgical procedure to decrease recurrence would have been cauterization.

(continued)

5. A 30-year-old nullipara, not wanting conception, presents for evaluation because of a recent experience of dyschezia during menses and deep dyspareunia. At vaginal examination, a 3-cm painful, fibrotic and nodular plaque is palpated in the posterior fornix. You diagnose vaginal endometriosis and recommend which one of the following?

    a. Immediate surgery in order to ameliorate reproductive performance in the future.
    b. Low anterior rectal resection to avoid bowel occlusion.
    c. Definitive surgery to prevent ureteral stenosis caused by the invariably progressive nature of the lesion.
    d. Conservative surgery at laparoscopy or laparotomy because medical treatment is definitely not effective in rectovaginal endometriosis.
    e. Use of low-dose, continuous oral norethindrone acetate, provided vaginal biopsy does not identify atypia, obstructive uropathy is ruled out, and the patient is informed that medical therapy is not curative.

6. A 45-year-old nulligravida undergoes laparoscopic excision of a 6-cm left ovarian endometriotic cyst. Histologic examination reveals cytoarchitectural and cytologic atypia. She denies desire for pregnancy. You advise which one of the following?

    a. Her risk of ovarian cancer would increase if she were to use postmenopausal hormone therapy.
    b. Her risk of endometrial cancer is increased and endometrial biopsy is warranted.
    c. Her risk of ovarian cancer is not substantially increased, but performance of transvaginal ultrasonography and evaluation of CA125 serum level at yearly intervals is suggested.
    d. Her risk of ovarian cancer is substantially increased and bilateral salpingo-oophorectomy is strongly recommended.
    e. Her overall cancer risk is increased and in-depth, systematic investigations regarding all organ systems should be performed.

7. Which one of the following is true about robotic-assisted surgery?

    a. Haptic (tactile) feedback is less realistic than conventional laparoscopy.
    b. Depth perception through the stereoscopic viewer is decreased.
    c. Seven degrees of movement is less than human wrist movement.
    d. Tremor filtration and motion scaling are limited to large movements.
    e. The surgeon must stand to control the robotic arms and perform surgery.