Clinical Management of Endometriosis – From Mild to Severe (Didactic)

PROGRAM CHAIR
Emilio O. Fernandez, MD

PROGRAM CO-CHAIR
Carlos Fernandez Ossadey, MD

Marc R. Laufer, MD          Paulo Ayrosa Ribeiro, MD          John F. Steege, MD
Radha Syed, MD               Fulvio Zullo, MD

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Endometriosis is a complex disease. Although recognized for many years, its clinical management still represents a great challenge for gynecologists. The diagnosis of endometriosis is usually delayed, leading to the compromise of nearby structures and organs with devastating consequences, which may adversely affect the patient’s quality of life and reproductive potential. Reviewing basic aspects of the physiopathology will help you understand how endometriosis progresses and how to explain its multiple clinical manifestations. Considering these fundamentals will improve your clinical approach in order to construct a better preoperative evaluation. This will play a pivotal role in dimensioning the extent and severity of the disease, which in turn will help you to structure an adequate clinical management.

**Learning Objectives:** At the conclusion of the course the clinician will be able to: 1) Describe the essentials of physiopathology and how they explain progression and clinical manifestation of the disease; 2) discuss how to do an early diagnosis using the adequate tools; 3) review the different alternatives for the surgical treatment of the disease; 4) discuss how to approach the pelvis in severe cases; 5) identify surgical strategies for endometrioma, avoiding ovarian damage; 6) discuss strategies to optimize fertility after surgery “The Fertility Window;” and 7) discuss how to manage pain to improve quality of life.

**Course Outline**

1:30 Welcome, Introductions and Course Overview  
E.O. Fernandez

1:35 Endometriosis as a Progressive Disease: Understanding the Pathogenesis of Endometriosis in Order to Develop Strategies to Diagnose and Treat the Disease  
F. Zullo

2:00 How to Diagnose the Endometriosis: Which Are the Modern Tools to Have a Precocious Diagnosis?  
C. Fernandez Ossadey

2:25 Surgical Treatment: Radical towards Disease and Conservative towards Function  
P.A. Ribeiro

2:50 Specific Strategy and Techniques: Cul de Sac Endometriosis  
F. Zullo

3:15 Questions & Answers  
All Faculty

3:25 Break

3:40 Endometrioma Management for the Generalist: How to Maximize Ovarian Preservation  
R. Syed

4:05 Infertility: How to Manage an Adequate Fertility Window after Surgery  
E.O. Fernandez
4:30  Pain: How to Be Successful in the Long Term in Patients with Endometriosis and Pain  
      J.F. Steege
4:55  Adolescent Endometriosis and Early Diagnosis  
      M.R. Laufer
5:20  Questions & Answers  
      All Faculty
5:30  Course Evaluation/Adjourn
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Linda Michels, Executive Director, AAGL*
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Consultant: Neosurgical
Speakers Bureau: Myriad Genetics Lab
Fulvio Zullo*

Asterisk (*) denotes no financial relationships to disclose.
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Endometriosis: A very ancient disease..

The first references to endometriosis-associated symptoms are found in the Ebers Papyrus (Egypt, 1500 B.C.), in which a treatment for a “painful discharge of menstruation” is described.

Nevertheless, a unifying theory regarding the origin of endometriosis has remained mysteriously elusive.

It is well defined as an inflammatory, estrogen-dependent condition associated with pelvic pain and infertility.

Endometriosis is not necessarily a progressive disease. In several instances, it persists as a minimal or mild disease, or it can resolve on its own.

Deep endometriosis should not be considered a progressive disease.

Pathogenesis of endometriosis: molecular hallmarks

Although retrograde menstruation is supported by multiple lines of scientific evidence and explains the physical displacement of endometrial fragments into the peritoneal cavity, additional steps are necessary for the development of endometriotic implants.

Pathogensis of Endometriosis in order to Develop Strategies to Diagnose and Treat the Disease

Financial disclosure

Objective

At the end of this session, participants will:

1. Have briefly reviewed the pathogenetic theories of endometriosis and how they explain progression and clinical manifestation of the disease.
2. Be aware that the knowledge of pathogenesis could help surgeons to identify a patient-oriented treatment with a reliable and precocious non-surgical diagnosis, an early medical management of pain, and a wise and safe surgical approach.
In women with endometriosis, there is an aberrant CC chemokines response to sex steroids both in their stroma and in microvascular endothelium.

E2 production and Inflammation

High levels of local estradiol and prostaglandin E2 (PGE2) are maintained in endometriotic tissue by autoregulatory positive-feedback mechanisms that involve nuclear receptors [SF1] and estrogen receptor β [ER-β], enzymatic pathways, cytokines, and growth factors.

PGE2 stimulates the expression of all genes such as 5αR and CYP17A1 necessary to enable the endometriotic stromal cell to synthesize estradiol from cholesterol.

A link between inflammation and estrogen production in endometriosis is substantiated by a feedback cycle that favors the overexpression of key steroidogenic genes, overexpression of COX-2, and continuous local production of estradiol and PGE2 in endometriotic tissue.

Women with endometriosis have an aberrant CC chemokines response to sex steroids both in their stroma and in microvascular endothelium.

E2 dependence and P resistance

In addition to estrogen dependence, there is increasing evidence to support a profile of P resistance in the pathophysiology of endometriosis.

Endometriotic lesions exhibit an overall reduction in P receptor expression relative to eutopic endometrium and an absence of P receptor-B.

Additionally, endometrial expression profiling has documented dysregulation of P-responsive genes in the luteal phase.

Incomplete endometrial transition from the proliferative to secretory phase.

Enhancement of survival and implantation of refluxed endometrium.

These findings support the capacity of endometriotic lesions for E2 biosynthesis and substantiate treatments aimed at promoting a hypoestrogenic peritoneal microenvironment.

The central role of estrogen in the pathogenesis of pain

E2 has pro-inflammatory and anti-apoptotic effects that are exacerbated in endometriotic lesions.

INFLAMMATION

→ An increased number of activated macrophages

Cytokines and chemokines increased: MMD, TNF-α, IL-1β, IL-6, IL-8, RANTES and monocyte chemotactic protein-1

→ Higher levels of COX-2 and PGE2

→ TNF-α promotes endometrial cell production of E2 and PGE2

→ IL-1β increases production of PGE2, which activates steroidogenic acute regulatory protein and aromatases (E2)

ENDOMETRIAL CELL SURVIVAL

→ Up-regulation of gene BCL-2

→ Enhanced proliferation

→ Hereditary genomic alterations: a susceptibility locus in the regions of chromosome 1q44 and 7q15

→ Acquired genomic alterations: loss of heterozygosity and somatic mutation of gene PTEN

→ Aberrant DNA methylation of promoters of genes involved in normal endometrial P response with resulting P resistance

Pathogenesis of endometriosis: other mechanisms

E2 Production and Endometrial Cell Survival

In endometrial lesion physiological levels of E2 reinforce mechanisms of cell survival and proliferation through the up-regulation of anti-apoptotic (BCL-2) and the down-regulation of pro-apoptotic genes (PTEN).

The increased sensitivity of endometriotic cells to the survival message mediated by E2 appears to be related to the up-regulated ERβ.

High levels of ERβ suppress E2.

High Erβ to ERα ratio suppresses PR and increases COX-2 levels contributing to P resistance and inflammation.

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**E₂ Production and Endometrial Cell Survival**

- Estrogens induce a rapid activation of the E₂-protein kinase B, or Akt, which plays a central role in endometriosis by increasing cell survival through decreased apoptosis.

- The constitutive shedding of resistant to lysis by NK cells.

- Larger tissue fragments have an increased capacity to implant owing to the continuous local stimulation of EIs due to intraluminal production of estradiol.

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**Pathogenesis of endometriosis: other mechanisms**

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**Immune clearance escape**

- Larger tissue fragments have an increased capacity to implant owing to the protection from immune clearance.

- The ectopic endometrium is more resistant to lysis by NK cells than the eutopic one.

- The constitutive shedding of ICAM-1 by ESCs is the potential mechanism through these cells escape NK cell-mediated clearance.

- A high concordance of autoimmune and atopic disease.

**Estrogens and immune clearance escape**

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Pathogenesis of endometriosis: other mechanisms

The extracellular matrix (ECM) contains proteins that are involved in the induction and progression of endometriosis. The matrix proteins, such as POSTN, OPN, and serpin E3 have been implicated in the progression of endometriosis.

All active peritoneal endometriotic lesions showed strong expression for each of the ECM proteins studied.

Endometriotic lesions can develop their own nerve supply, thereby creating a direct and two-way interaction between lesions and the CNS. The severity of pain associated with endometriosis is modulated by E2, P, and P. These hormones influence the growth of endometriotic lesions and the pain associated with them.

Pathogenesis of endometriosis

If the nociceptive stimulation lasts over time, modifications in the neural circuits are created with specific pattern of functional brain activation and brain anatomical reorganization that contribute to the chronicity of the pain and even to an increase in its intensity.

NEO-ANGIOGENESIS

- IL-8 and TNF-a promote proliferation and adhesion of endometrial cells and angiogenesis.
- VEGF is abundantly expressed in the glandular compartment of peritoneal implants of endometriosis, and is secreted by activated peritoneal macrophages.
- Other angiogenic factors implicated in disease pathophysiology include angiogens, PDGF, and MMP.

In addition, nerves frequently accompany angiogenesis (NEUROANGIOGENESIS), likely contributing to the pain associated with this disorder.

Pathogenesis of endometriosis: other mechanisms

POSTN is overexpressed in the endometrial and ectopic endometrium with endometriosis and a cycle variation of POSTN levels was observed.

A role of POSTN in the pathophysiology of endometriosis was suggested.

From pathogenesis to treatment

Given the evidence that the ectopic endometrium is modulated by E2 and P, however, current medical management of endometriosis is based on hormones, acting by two main mechanisms:

- Pseudopregnancy to create a pseudodecidualization of the endometrium.
- GnRH agonists, GnRH antagonists, and aromatase inhibitors to reduce the tropism of endometriotic lesions.

Strategies to block E2 production and its effects are the mainstream of pharmacologic treatment of endometriosis.
Pain relief after the administration of GnRH-agonist for a period of 3–6 months can be used as an "ex adiuvantibus" confirmation of catamenial ethiology.

By reducing estrogen levels to the lowest possible, GnRH-agonists are the most effective antiinflammatory molecules for the treatment of pain. Their effect is exerted by reducing estrogen-mediated inflammation and cell survival promotion.

GnRH-agonists allow both therapeutic and diagnostic use of this device!!!


How to Diagnose Endometriosis

Which are the modern tools to have a precocious diagnosis?

Fernández Carlos MD & Albornoz Jaime MD
Clinica Las Condes, Chile

Disclosure

Stockholder: IMH Ltda.

Objective

• To discuss how to do an early diagnosis using the adequate tools.

Why is it important to diagnose Endometriosis in an early stage?

• Endometriosis can be a progressive disease in up to 50% of patients.

"Hoaghe Hum Reprod Update 2002"

• Early non-invasive diagnosis has the potential to offer early treatment and prevent progression.
Progression will compromise...

- Quality of life
- Reproductive potential

Nevertheless, diagnosis is delayed...

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Time Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979 - 1984</td>
<td>9.2 years</td>
</tr>
<tr>
<td>1984 - 1990</td>
<td>4.6 years</td>
</tr>
</tbody>
</table>

- What’s the delay? A qualitative Study of women experiences of reaching a diagnosis of endometriosis.
  - Ballard K, Fertil Steril 2006
- Time elapsed from onset of symptoms to diagnosis of endometriosis in a cohort study of brazilian women.
  - Arruda M. Hum Reprod 2010

Why diagnosis is delayed...

- Lack of awareness of the disease
- Poor understanding of the disease

Causes

- Patient level
  - “Inability to make clear distinctions between normal and abnormal menstrual experiences”
- Medical level
  - Pain normalized by family doctors
  - Intermittent hormonal suppression of symptoms
  - Use of nondiscriminatory investigations

The availability of a non-invasive tool to evaluate the likelihood of finding endometriosis at laparoscopy could reduce the diagnostic delay and the number of women undergoing surgery unnecessarily.

Future tools to have a precocious diagnosis...

- Although CA 125, Citokines, Angiogenic and Growth Factors, all show altered levels in the peripheral blood of women with endometriosis when compared to controls.
- Thus far neither a single biomarker nor a panel of biomarkers has been validated for clinical use as a diagnostic test in women with endometriosis.
How can we improve our diagnosis

- Symptoms
- High risk groups
- Physical examination
- Ultrasound
- Magnetic Resonance Imaging

What kind of pain

- Chronic pain - is the most frequent, but not specific.
- Dysmenorrhoea - progressive both in length and severity.
- Progression of dysmenorrhoea to the perineal region - is almost diagnostic of DIE.
- Dyspareunia - in case of infiltration of the cul-de-sac structures.
- Dyschesia - in cases of bowel endometriosis
- Dysuria in association to hematuria - is highly indicative of DIE.

Can specific pain symptoms help in the diagnosis of endometriosis?

A cohort study in women with chronic pelvic pain.

Ballard K. Fertil Steril 2010

- “women with endometriosis are more likely to report their pain as throbbing and are more likely to experience dyschesia when compared with women with an apparent normal pelvis”
- “Currently is not possible to triage women with chronic pelvic pain effectively on history alone”
- “Women deserve referral to a specialized center”
Routine vaginal examination alone might be insufficient to detect endometriosis before laparoscopy

- “Although digital vaginal examination may be successful in detecting painful nodules in the posterior cul de sac or along the uterosacral ligaments, for many patients physical examination may not reveal abnormalities”

Hudelist G, Ultrasound OG 2011

Hooghe TM, Gynecol Obstet Invest 2006
• **Laparoscopy**

**Imaging**

**Transvaginal Ultrasound**

- Is an adequate diagnostic method for detecting ovarian endometriotic cysts...
- It may be useful in detecting DIE located in the rectovaginal septum...
- It does not rule out peritoneal endometriosis and endometriosis-associated adhesions.

*Moore J, Ultrasound OG 2002*
*Kennedy S, Hum Reprod 2005*
*Bazot M, Fertil Steril 2009*

**Transrectal Ultrasound**

- Provides information regarding the degree of invasion of the rectal wall in case of rectal infiltration by DIE

*Kennedy S, Hum Reprod 2005*

**Magnetic Resonance Imaging (MRI)**

- Useful in cases of high-degree of suspicion of DIE.
- Provides valuable information about the specific location and extension of the disease.
- In case of high probability of bowel endometriosis, it can help to plan the surgical strategy.
Conclusions...

- Aware
- History
- Pelvic examination
- Imaging
- Laparoscopy

Pelvic Surgeon

References


• Luciana Pardini Chamié, MD, PhD • Roberto Blasbalg, MD, PhD • Ricardo Mendes Alves Pereira, MD Gisele Warmbrand, MD, PhD • Paulo Cesar Serafini, MD, PhD. Multiplexed protein measurement: technologies and applications of proteins and antibody arrays. Nat Rev Drug Discov 2006;5:510–20.


• Luciana Pardini Chamié, MD, PhD • Roberto Blasbalg, MD, PhD • Ricardo Mendes Alves Pereira, MD • Gisele Warmbrand, MD, PhD • Paulo Cesar Serafini, MD, PhD. Multiplexed protein measurement: technologies and applications of proteins and antibody arrays. Nat Rev Drug Discov 2006;5:510–20.
Surgical Treatment of Deep Endometriosis

Radical Towards Disease and Conservative towards Function

Prof. Dr. Paulo Ayroza Ribeiro, M.D.

Disclosure

- Consultant: Covidien
- Speakers Bureau: Bayer-Sherring, Covidien

Objectives

- At the conclusion of this activity, the participant will be able to list and compare the value of preservation to adjust the radicality in the surgical treatment of deep endometriosis

Concept

- Surgical Treatment: Gold Standard
- Nodule Excision: Gold Standard
- Fertility Sparing: mandatory
Conservative

Radical

• Problem

Radicality

Complication

Urinary and Rectal Disfunction in Deep Endometriosis Surgical Treatment

• Urinary (16-80%)
  – Sensitive loss
  – Bladder distention reduction
  – Urgency
  – Voiding difficulty
  – Post miccional
  – Hipotony
  – vesico-urethral reflux

• Rectal (0-3.4%)
  – Sensitive loss
  – Urgency
  – Incontinence
  – Constipacy
  – Dificuldade na diferenciação entre flatos e fezes
  – Reduction of rectal sensibility

Nerve Sparing in Deep Endometriosis Surgery

• 1st case of urinary retention
• Anxiety
• Searching for knowledge
• A decade dedicated to that theme

Nerve Sparing in Deep Endometriosis Surgery
“There is no uterosacral ligament, but a network of sympathetic and parasimpathetic nerve fibers”
Possover, M (2003)

Objective. To decrease postoperative morbidity associated with radical hysterectomy Rutledge type III, we identified the parasympathetic innervation of the bladder in the cardinal ligament.

Conclusion. Using the middle rectal artery as a landmark the neural part of the cardinal ligament can be preserved, resulting in preservation of the motor function of the bladder.

Laparoscopically assisted vaginal resection of rectovaginal endometriosis
Marc Possover, MD, Herbert Diebolder, MD, Karin Plaul, MD, and Achim Schneider, MD, MPH

Technique: The procedure is started by vaginally excising the involved area which is left on the rectum, followed by bilateral dissection of the pararectal and retrorectal spaces. Para- and retrosigmoido-rectal spaces are developed laparoscopically along the coccygeosacral bone and medially to the pelvic splanchnic nerves —

Conclusion: The combination of laparoscopic and vaginal approaches is useful for removing extensive endometriotic infiltration of the rectosigmoid; bladder and rectal function and fertility can be preserved.

Radical towards disease ...

...Conservative towards function

Balance is the Key to Life
Conservative
- Uterus
- Tubes
- Ovary
- Nerves

Conservative to the Nerves
- Knowledge
- Identification
- Preservation

• Nerve Sparing
  - Reduce urinary and rectal functional complications
  - Reduce surgical trauma
  - Adjust surgical radicality to the patients needs
Case Report

Hydrenephrosis + hydrourether bilat.

Laparoscopic nerve-sparing transperitoneal approach for endometriosis infiltrating the pelvic wall and somatic nerves: anatomical considerations and surgical technique

Surgical technique

We describe two different laparoscopic transperitoneal approaches to the lateral pelvic wall in case of: (A) deep pelvic endometriosis with rectal and/or parametral involvement extending to pelvic wall and somatic nerve; (B) isolated endometriosis of pelvic wall and somatic nerves [11].

Laparoscopic nerve-sparing surgery of deep infiltrating endometriosis: description of the technique and patients’ outcome

We describe two different laparoscopic transperitoneal approaches to the lateral pelvic wall in case of: (A) deep pelvic endometriosis with rectal and/or parametral involvement extending to pelvic wall and somatic nerve; (B) isolated endometriosis of pelvic wall and somatic nerves [11].

- No significant difference was found in SHOW-Q scores between patients submitted to intestinal resection and patients submitted to intestinal nodule excision (P>0.05).
- Six months after surgery and postoperative COC treatment, a significant improvement was observed in the SHOW-Q domains of pelvic problem interference, sexual satisfaction and desire (P<0.05).

Mabrouk, M., et al. (2012)

- Both groups had better post-operative outcomes when compared with the preoperative assessments.
- Mean BDI and DAS levels were comparable with the normal population.
- Overall assessment points, the bowel resection patients had better outcomes for DAS (P < 0.05) and SSFS’ ‘arousal’ (P < 0.05) than the no bowel resection patients.
- Radical surgery for endometriosis in both groups improved the levels of depression and sexual functioning, but only the bowel resection patients showed improvements in relationship satisfaction.


What is Nerve Sparing?

- Nerve Sparing
- Neurolisis
- Pelvic Neuro Surgery (Neuropelveology)
• Nerve Sparing
• Neurolisis
  • Neuropelveology

Surgical Treatment of Endometriosis

• Nerve Sparing
  • Neurolisis - nodules
    – somatic
      • Pudendal
      • Sciatic
      • Obturator
      • Femoral
    – autonomic

• Nerve Sparing Classifcation
  – Superior Hipogastric Plexus + Hipogastric Nerves
  – Inferior Hipogastric Plexus
  – Pelvic Splanic Nerves

• VIDEO

• Level of Preservation
  – Inferior Hypogastric Plexus
• VIDEO

• Level of Preservation
  – Pelvic Splanchnic Nerves

• VIDEO

• VIDEO
Nerve Sparing Surgical philosophy Respect
References


Specific Strategy and Techniques: Cul de Sac Endometriosis

Fulvio Zullo
Maggiore Grandi University of Camerino
Italy

Clinical Management of Endometriosis – From Mild to Severe

Specific Strategy and Techniques: Cul de Sac Endometriosis

Fulvio Zullo
Maggiore Grandi University of Camerino
Italy

Endometriosis: A multifaceted disease...

Cul de Sac Endometriosis

A correct description 80 years old

Kissing ovaries

Superficial endometriosis

Deep endometriosis

The cul-de-sac obliteration was defined as "extensive adhesions in the cul-de-sac obliterating its lower portion and uniting the cervix or the lower portion of the uterus to the rectum, with adenoma of the endometrial type involving the cervical and the uterine tissue and probably also the anterior wall of the rectum."

Sampson et al., Am J Obstet Gynecol 1925

Specific Strategy and Techniques: Cul de Sac Endometriosis

Financial disclosure

I have no financial relationship to disclose

Objective

At the end of this session, participants will:

1. Have briefly reviewed the specific surgical techniques to deal with all forms of Cul the Sac Endometriosis (superficial endometriosis, kissing ovaries and deep endometriosis).
2. Be aware that deep endometriosis is a delicate surgical indication and the whole management should include an early non-surgical diagnosis and an adequate integration with medical treatment.

Endometriosis in Rokitansky patients, male endometriosis as well as in any location along the migration pathway of the embryonic mullerian system.

Sampson et al., Am J Obstet Gynecol 1925

The theory of mullerianosis and deep endometriosis

Ovarian steroids

DIE, endometriosis in Rokitansky patients, male endometriosis

Embryonic Mullerianosis explains...

DIE, endometriosis in Rokitansky patients, male endometriosis

with different theories on pathogenesis

Adenomyosis

Ovarian endometriosis

Peritoneal endometriosis

Deep endometriosis

Peritoneal and ovarian endometriosis, adenomyosis

Retrograde menstruation explains...

DIE, endometriosis in Rokitansky patients, male endometriosis

as well as in any location along the migration pathway of the embryonic mullerian system.

Sampson et al., Am J Obstet Gynecol 2013

Deep endometriosis has a different histology

Ovarian steroids

The nodule is not the consequence of deep-infiltrating endometriosis but is the same as an adenomyotic nodule.

A transition from minimal or mild to deep endometriosis was never observed.

Deep endometriosis should not be considered a progressive disease.

Sampson et al., Am J Obstet Gynecol 2013

Minimal or mild peritoneal lesions, so frequent they should be considered a physiological endometriosis, usually resolve spontaneously!!

Sampson et al., Am J Obstet Gynecol 2013

4 benign mullerian diseases: adenomyosis, deep endometriosis, endosalpingiosis, endocervicosis

Hoxa and regulation

Wnt

Nfe2l3

Deregulation affect cell migration and differentiation of Mullerian structures determining a misplacing of the embryonic mullerian tissue

Sampson et al., Am J Obstet Gynecol 2013

Sampson et al., Am J Obstet Gynecol 2013

Sampson et al., Am J Obstet Gynecol 2013

Sampson et al., Am J Obstet Gynecol 2013

Sampson et al., Am J Obstet Gynecol 2013

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Sampson et al., Am J Obstet Gynecol 2013

Sampson et al., Am J Obstet Gynecol 2013

Sampson et al., Am J Obstet Gynecol 2013

Sampson et al., Am J Obstet Gynecol 2013
Diagnostic strategies for cul de sac endometriosis

When it should be suspected?

- Suspicious signs
  - Dysmenorrhea (90%)
  - Severe chronic pain (60%)
  - Dyschezia (40%)
  - Deep dyspareunia (35%)
  - Micturition (20%)

- Pathognomonic signs
  - Nodules of the Douglas pouch are easily reached by the gynecologist’s examining fingers.

- Only a 5% are pain free!!

- Pain relief after the administration of GnRH agonist for a period of 3-6 months can be used as an “ex aduvantibus” confirmation of catabolic etiology.

- Nodules at the site of the catabolic process.

- The main clinical hallmark...
  - The positive predictive value of severe dysmenorrhea with nodularity of the cul-de-sac and/or uterosacral ligaments was 94.0%.

- Unfortunately, they are also occasional.


Is deep endometriosis always an absolute and immediate surgical indication?

- Treatment of pelvic pain associated with endometriosis

- GnRH-a, P, AIs for 6-12 months

- Pain relief (60-90%)
- Lesion reduction (30%)
- Health related-quality of life improvement
- Patient satisfaction

- Appropriate surgical timing in order to attempt conception shortly after surgery

- Post-operative pain and lesion recurrence reduction

- Versaldobro V, et al., Hum Reprod 2009

- Koninckx et al., Hum Reprod 2012

- De Vos et al., Fertil Steril 2013

- Medical treatment for cul de sac endometriosis

- Aromatase and steroidal acute regulatory protein (SIAT), leading to a local E2 and P biosynthesis, are overexpressed in endometriosis

- ER and PR were observed in the smooth muscle component of DIE, cycle’s phases independently, except colonic endometriosis, where ER were absent.

- Elevated local levels of E2 promote the growth of smooth muscle fibers in the endometriotic lesions and induce cell survival and immune alteration.

- Nael et al., Fertil Steril 2010

- Anti-inflammatory and anti-proliferative

- Suppression of receptors expression in the smooth muscle cells

- Malek et al., ISRN Gynecol 2011

- Surgical treatment of the Cul de sac endometriosis

- Supercificial endometriosis

- Excision of the small lesion involving superficially the utero-sacral ligament

- A superficial lesion could not be a progressive disease.
- A transition to deep infiltrating disease is highly unlikely.

- Kuentz et al., Fertil Steril 2012

- Acien et al., Fertil Steril 2013

- Koninckx et al., Fertil Steril 2012

- Acien et al., Hum Reprod 2011

- If surgery is required for severe pelvic pain unresponsive to medical treatment, the surgical excision of the lesion seems to be the best strategy.
Surgical treatment of the Cul de sac endometriosis

**Kissing ovaries (Most severe ovarian endometriosis)**

**Severe Pelvic Pain**
- Unresponsive to medical treatment

**Reproductive desire**

In the most severe form of endometriosis, both ovaries are cystic, thickened, and adhere to the posterior side of the uterus and to the broad and uterosacral ligaments.

**Peritoneal fluid**
- Inflammation triggered

- Adhesion between the adjacent peritoneal surfaces and organs
- Ovaries are displaced medially and caudally into the Douglas

**Indication to surgery**

Hormonal treatments must not be offered in the presence of obstructive uropathy, symptomatic bowel stenosis and adnexal mass of a doubtful nature.

---

**What’s the best surgical technique for the kissing ovaries?**

When US reveals the presence of kissing ovaries, the surgeon should expect to find a tangled pelvis with subverted anatomy.

**Severe Pelvic Pain**
- Unresponsive to medical treatment

**Reproductive desire**

- Inclusion of the ovarian capsule by cold scissors.
- After cleavage plane identification, excision of the cyst by atraumatic dissection.
- Control of hemorrhage by means of bipolar forceps (40 W), coagulating only the sites of bleeding.
- Cyst removal from abdomen by endo-bag.

---

**Surgical treatment for Deep Endometriosis**

**What’s the best technique?**

The complete surgical management could be curative treating disease that cause pain...

- If DIE is only an external adenomyosis without typical lesions...
- It is NOT a progressive disease...
- It is close to impossible to remove all endometriotic cells from all sites...
- Surrounded fibrotic layer may be left behind...
- Pain may be related to Central Sensitization and Hyperalgesia...

---

**Surgical treatment for Deep Endometriosis**

**What’s the best technique?**

**Reproductive desire**

**Severe Pelvic Pain**
- Unresponsive to medical treatment

- Comparison of clinical outcome between different surgical techniques was not possible.

**Reproductive desire**

- Few studies of the 49 included in the review reported fertility (37%).
- No RCTs or meta-analyses are available.

---

**Deep Endometriosis: pain management**

In long-term noxious stimulation, there could be morphological changes of axons (e.g., sprouting), central synaptic connectivity, expression of receptor molecules, an altered descending modulatory system, and cortical processing.

**Central sensitization**
- Generalized hypersensitivity
- Chronicization of the pain

**All visceral pain must be managed as early as possible to avoid severe chronicization.**

---

**Surgical treatment of deeply infiltrating endometriosis with colorectal involvement**

**Reproductive desire**

**Severe Pelvic Pain**
- Unresponsive to medical treatment

- Comparison of clinical outcome between different surgical techniques was not possible.

**Reproductive desire**

- Few studies of the 49 included in the review reported fertility (37%).
- No RCTs or meta-analyses are available.
endometriotic nodule attached to the central area between the rectum and the posterior vaginal fornix.

Dissection of the ovary from the side wall. The aim should be to leave the endometriotic nodule attached to the central area between the rectum and the posterior vaginal fornix.

Recto-sigmoid lesions infiltrating deeper than the muscular layer of the bowel.

Deep lesions affecting the rectum up to the muscular layer of the bowel.

Classical Shaving

Monopolar delimitation of the nodule through the vagina. Dissection between the bowel and the side wall. Dissection of the ovary from the side wall.

Both uteruses need to be identified if close to or involved in the endometriotic nodule.

The aim should be to leave the endometriotic nodule attached to the central area between the rectum and the posterior vaginal fornix.

Reimbursement for resection is more higher than discoid excision

Bowel resection makes bowel surgeons co-responsible (DEFENSIVE MEDICINE)

Higher complications rate
- Leakage 3-5%
- Fistula 6-9%
- Infection 4-6%
- Bladder, sexual and bowel dysfunctions 2-4%
- Repeat surgery 10%
- Recurrence rate 1%

Deep sigmoid nodules
- Deep and large (>3cm and >1/3 of circumference) rectal nodules
- Multifocal

Technically more demanding
- Slower

Low complications rate
- Leakage 0.1%
- Fistula 0.1%
- Infection <1%
- Bladder, sexual and bowel dysfunctions <3%
- Repeat surgery <1%
- Recurrence rate 1%

Deep sigmoid nodules
- Deep and large (>3cm and >1/3 of circumference) rectal nodules
- Multifocal

Technically more demanding
- Slower

What’s the best surgical technique?

Bowel resection

Pros
- Lower complications rate
- Higher complications rate

Cons
- Leakage 3-5%
- Fistula 6-9%
- Infection 4-6%
- Bladder, sexual and bowel dysfunctions 2-4%
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Reimbursement for resection is more higher than discoid excision

Bowel resection makes bowel surgeons co-responsible (DEFENSIVE MEDICINE)
Deep endometriosis is a specific non-progressive disease having its own pathogenesis and histology.

Clinical examination remains the key strategy to suspecting disease and deciding to perform surgery.

Medical and surgical treatment are two effective approaches not mutually exclusive.

Bowel resection for Deep Endometriosis

No differences between bowel resection and discoid excision in the early steps.

Opening of the mesorectum adjacent to the sacral promontory and dissection in a caudal direction. Opening the peritoneal layer lateral to the rectum on the right side.

Identification of the healthy area in the rectovaginal septum, distal to the intestinal DIE lesion. Cranial dissection of mesorectum and mobilization of left parietocolic gutter.

Specific Strategy and Techniques: Cul de Sacs Endometriosis

Take home messages

Deep endometriosis is a specific non-progressive disease having its own pathogenesis and histology.

Clinical examination remains the key strategy to suspecting disease and deciding to perform surgery.

Medical and surgical treatment are two effective approaches not mutually exclusive.

References (1):

PG111
Clinical Management of Endometriosis – From Mild to Severe (Didactic)
Specific Strategy and Techniques: Cul de Sac Endometriosis

THANKS FOR KIND ATTENTION!!!

Prof. Fulvio Zullo
Department of Obstetrics and Gynaecology
"Magna Graecia" University of Catanzaro
LEARNING OBJECTIVES

- At the end of this presentation, participant will be able to:
- Define endometrioma
- Describe the Etiology and pathogenesis of endometrioma
- Review Management strategies
- Discuss Surgical Vs Medical management
- Discuss Implications of treating vs non treatment
- Identify Risk of malignancy in Endometrioma

DEFINITION OF ENDOMETRIOMA

- Also called “Chocolate Cysts”, Endometrioma is a grossly hemorrhagic cyst formed out of a follicular or corpus luteal cyst secondarily invaginated with Endometriotic cells from surface of the ovary into the cyst wall-inflammation and scarring causes adhesion to surrounding structures like pouch of Douglas and broad ligament. As it enlarges, endometrioma can rupture implanting further endometriotic glands in the pelvis (1,2,3) (Histological studies by various authors have proved this theory).
- Most commonly encountered dx in ovarian sx /present in 17-44% of pts w/endo (4)

ETIOLOGY AND PATHOGENESIS

- 1921-Sampson noted varied histology in different areas of Endometrioma including functional luteal membrane and ovarian epithelium
- 1979-Czernobilsky&Morris-described a variety of epithelium in endometrioma
- Nisolle-pochet:1988-113 cases histological evidence of typical glandular epith and stroma of endometrial glds before and after hormonal rx(18%-cyst lining only,47% oviduct like epith w/cilia,others-flattened epith and gld and stroma of endomet)
- 1990-Martin&Berry-41 choc cysts-61% microscopically proven endo,27% C.Luteal cysts
- 1991-Vercillini et al-confirmed 97.7% of visual dx of Endo Cysts histologically-endomet glds,endomet stroma,hemosiderin laden macrophage,or endomet like glds
- 1991-Fayez &Vogel-found NO endomet lining in 66 endomet Cysts out of 50 pts-either inadeq sampling or 2nd theory of celomic metaplasia
Etiology and Pathogenesis

- 1992-Nezhat et al-Classified into 2 major types-Small Type I-1-2 cm pure endometriomas contain dark fluid develop from surface Endo-histology proven
- Type II A-Large Endo Cysts-cyst wall can be easily separated-implants do not penetrate cysts-follicular or luteal origin
- Type II B/C-functional cysts deeply involved w/surface endometriosis-excision more diff due to adhesions at deep implants
- Pathogenesis and Physiopathology of endometriomas remain widely debated

Pathology

- Variable morphology of Endometrioma characterizes the debate on Histogenesis of the entity
- Presence of Endomet Glands and stroma though a must for dx ,other pathology may exist- like hemosiderin laden macrophages-endometrial lining alone w/o stroma or stroma w/o lining,hemorrhagic Corpus Luteum or Follicular cysts with hemorrhage

Pathology/Histogenesis

- Ridley reviewed the theories on histogenesis of Endometriosis
- A)Transplantation(transplantation and metaplasia and growth of Mullerian rests can be best explained by Sampson’s Theory)
- B)Celomic Metaplasia
- C)Metaplasia induced by factors introduced into peritoneum

Diagnosis of Endometrioma

- S/S-Dysmenorrhea,Chr Pelvic pain,Dyspareunia,Infertility
- Redwine reported 100% of pts w/endo Cysts had pelvic or Intestinal endo-advanced disease
- Exam: Pelvic tenderness/Mass adherent to uterus
- Sonography:has dramatically improved the dx of ov endo-providing reliable criteria for sx-Kurjak et al,Valentin et al

Biomarkers/Malignancy

- CA125-frequently elevated-low specificity-also elevated in non-endo ca like endometrial ca,pancreatic,lung,breast and colorectal,TB,Cirrhosis,pregnancy,menses can raise value
- Newer-Circulating miRNA (Wang et al)
- CALD1(Meola et al)
- Suspicious for malignancy: markers used
- HE4/CA72-4-are used to separate clinically suspected endo cysts from malignancy(Manuela Anastasi et al)
- Commercially available-OVA1/ROMA are using several markers to distinguish benign endo cysts from malignancy

Diagnosis-2-SONO

- U/S morphology-Zupi et al described:
- Round homogeneous ,hypoechoic low level echoes w/w/o int septa/no vascularization of capsule
- As above w/echogenic portion
- As above w/thin internal trabeculations
- Adhesions suspected w/probe and palpation -to ut/broad lig/Rectovag/bladder
- AFS(revised 1985) classification uses size and laterality of u/s dx cysts to classify severity of endo
Final Diagnosis/Management - Surgery

- Laparoscopy is the procedure of choice for Dx and Mgt of Endometriotic Cysts (Nezhat et al) (13)
- Medical mgt proven ineffective
- Simplest Technique - Fenestration and drainage of "chocolate cyst" - 50% recurrence rate (Nezhat et al)
- Puncture and aspiration of cyst with washing of capsule ineffective (Vercillini et al) (14)
- Hasson (15) - simple aspiration and drainage - 8/9 endometrioma recurred

Surgical Technique

- Nezhat et al have advocated: (15)
- Small (Type I): (surface cystic lesions) Endometrioma - Diff to remove-biopsy and drain and vaporize w/CO2 laser or bipolar coag
- Larger Type I lesions - must excise completely
- Type II A (c.lut like or follicular w/endo): Lyse adhesion of Ov/evaluate cortex/open cyst wall and eval/bx wall

Surgical Technique - 2

- Type II B/C (functional cysts involved deeply with Endo) w/severe adhesions: diff to remove - Lyse adhesions/develop plane betw cyst wall and capsule w/hydro-strip cyst wall/control bleeding at hilum w/bipolar
- Redundant ov tissue sutured (4/0 polydaxon) from inside to avoid adhesions/bipolar for bleeders
- Development of plane by hydro avoids rem of healthy ov follicles preserving fertility potential

Video Clip

- Courtesy Nezhat et al

Impact of Surgery on Fertility

- Y.M. Hwu et al studied 1642 pts of Lap ov cystectomy in endo cysts for infertility in a retrospective analysis. AMH levels were measured preop and 3mos postop as biomarkers for ov reserve
- Control grp of 1323 pts of ov cystectomy w/o endometrioma
- Conclusion: Both Ov endometrioma and cystectomy cause sig reduction in ov reserve - Bilat endometriomas cause a profound neg impact on ov reserve vs unilat regardless of conserv/sx

Impact of Surgery on Fertility

- Important to counsel pt w/Endometrioma w/poor ov reserve prior to sx - ov failure after sx may occur
- AMH can be considered as a preop routine test prior to Endometrioma sx
- Considered a more universal test than Antral Follicle count (AFC)
Endometrioma and Malig potential

- Y. Higashiura, Kobayashi et al. did a review of lit. to investigate malig transf of Endo-483 pts from 1966-2011-89% Epith Ov Ca and 11% mesenchymal ca
- Several immune factors are modified in endo lesions/eutopic endomet-endomet is an inflam condition w/dysregulated immune response
- Higher incidence of melanoma, nonhodgkins, endomet ca, breast ca in pts w/endomet

Malignancy and Endo-2

- Endo assoc with synchronous endomet ca/ov ca
- Mabrouk et al.-mixed clear cell ca/endometrioid adeno ca arising from DIE asso w/ endometrioid adeno ca of endometrium
- Malig transf incidence 0.6-0.8%
- Associated malig in Endo-EOC/other Mullerian type (MMBT, SBT, LG-ET)/Sarcomas

Summary

- Endometriosis is complex and needs careful evaluation prior to treatment considering most will present for infertility
- Ovarian reserve must be preserved for fertility potential when contemplating sx
- Lap ov cystectomy is the procedure of choice
- Consider AMH eval preop and postop
- Rule out malignancy prior to sx
- Consider the higher risk of malig in Endo/also assoc malignancies
Infertility: How to Manage an Adequate Fertility Window after Surgery

Emilio Fernández MD, Jaime Albornoz MD.
Clinica Las Condes - Chile

Disclosure

I have no financial relationships to disclose.

Objective:

• To Discuss strategies to optimize fertility after surgery during “The Fertility Window”.

Endometriosis and infertility

• “The Infertility specialist when approaching Endometriosis needs to answer three fundamental questions”:
  • Why endometriosis cause infertility?
  • How are we going to treat the disease?
  • What for? To get the patient pregnant...

Endometriosis and Infertility

Why?

• By compromising the reproductive environment by a dramatic immune-inflammatory reaction and the disruption of the anatomy of the reproductive organs, endometriosis cause infertility.

Endometriosis and Infertility: Mechanisms

Role of inflammatory mediators:

- Alteration of follicular development
- Disruption of ovulation and oocyte quality
- Lower Fertilization rate
- Poorer embryo quality
- Alteration of tubal transport
- Lower Implantation rate

Role of mechanical factors:

- Disruption of ovulation
- Alteration of ovum pick-up and tubal transport

Endometriosis and Infertility

How?

• By a maximal resection of the ectopic endometrial tissue (reducing the immune-inflammatory reaction) and by restoring the anatomy of the reproductive organs.

Endometriosis and Infertility

What for?

• TO OPEN A FERTILITY WINDOW

Can we predict fertility potential after surgery?

Fertility Predictive Factors

• Anatomical disruption of reproductive
  ✓ Endometriosis Fertility Index (EF)
  • Age
  • Infertility duration
• Ovarian reserve status (AMH, AFC, FSH) Concomitant Male and Immunological factors
• Access to Assisted Reproduction Techniques (ART)

Anatomical disruption of Reproductive Organs after surgery:

Endometriosis Fertility Index (EFI)

• Historical data:
  • Age
  • Duration of Infertility
  • Prior pregnancy
• AFS/ASRM Endometriosis Score
• Functional score at the conclusion of the surgery

Adamson, Endometriosis Fertility Index, Fertil & Steril 2009

ENDOMETRIOSIS FERTILITY INDEX (EFI)

<table>
<thead>
<tr>
<th>Factor Description</th>
<th>Points</th>
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<th>Points</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
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<td>Age</td>
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<tr>
<td>Prior pregnancy</td>
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<td>Yes</td>
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<td>No</td>
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</tr>
</tbody>
</table>

Historical Factors

Surgical Factors

EF = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS
EFI: Least Functional Score

Is an anatomical observation of the tube, fimbria and ovary at the end of the surgery

<table>
<thead>
<tr>
<th>Structure</th>
<th>Operative Term</th>
<th>Operative Description</th>
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</thead>
<tbody>
<tr>
<td>Tube</td>
<td>Mild</td>
<td>Minimal injury to tenia mucosal of the fallopian tube. Moderate limitation in motility.</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Moderate injury to tenia mucosal of the fallopian tube. Severe limitation in motility.</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Severe injury to tenia mucosal of the fallopian tube. Severe limitation in motility.</td>
</tr>
<tr>
<td>Fimbria</td>
<td>Mild</td>
<td>Minimal injury to fimbria with minimal scarring.</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Moderate injury to fimbria with minimal scarring.</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Severe injury to fimbria with severe scarring.</td>
</tr>
<tr>
<td>Ovary</td>
<td>Mild</td>
<td>Normal or almost normal ovarian size, minimal or minimal injury to ovarian serosa.</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Ovarian size reduced by two-third or more, moderate injury to ovarian serosa.</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Ovarian size reduced by two-third or more, severe injury to ovarian serosa.</td>
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</tbody>
</table>

Influence of Infertility duration over Conception

Pregnancy rate in IUI cycles according to duration of Infertility
Influence of Ovarian Reserve on Pregnancy Rate

Access to ART Treatment

ART Registry: Chile 2009

- Women population: 8,381,981
- Women in Reproductive Age (25-40 yo): 1,810,742
- Number of infertile women: 181,074
- Number of women requiring ART: 54,322
- ART cycles: 1,446 (2.7%)

So.......What can we do to manage adequately the Fertility Window?

Fertility Window

Time to spontaneous pregnancy after deep infiltrating endometriosis surgery

Reproductive performance in infertile women with colorectal endometriosis after surgery

- Fernandez E et al (Unpublished Data)
- Darai et al, Fertility and Sterility 2011
Fertility and clinical outcome after bowel resection in infertile women with endometriosis

Stepniewska et al, RBM Online 2010

Medical Therapies for Infertility Treatment:

*Intrauterine Insemination (IUI) Controlled Ovarian Stimulation*

- In infertile women with AFS/ASRN stage I/II endometriosis, clinicians may perform IUI with COS, instead of expectant management, as it increases live birth rate.

ESRHE Guideline for Endometriosis, 2013

Cicle fecundity in women with Stage I or II Endometriosis: COS and IUI results

ASRM Practice Committee, Fertility and Sterility 2012

Medical Therapies for Infertility Treatment:

*Intrauterine Insemination (IUI) Controlled Ovarian Stimulation*

- In infertile women with AFS/ASRN stage I/II endometriosis, clinicians may perform IUI with COS, instead of IUI alone, as it increases pregnancy rates.

ESRHE Guideline for Endometriosis, 2013

IVF: When?

- Low Endometriosis Fertility Index Score (EFI)
- Women > 35 years old
- Diminished Ovarian Reserve
- Male or Immunological Factors

ESRHE Guideline for Endometriosis, 2013

Assisted Reproduction Techniques:

*In vitro Fertilization (IVF)*

- IVF should be recommended for infertility associated with endometriosis, especially if tubal function is compromised or if there is male factor infertility, and/or other treatments have failed.

ESRHE Guideline for Endometriosis, 2013
In stage III/IV endometriosis, cumulative endometriosis recurrences are not increased after controlled ovarian stimulation for IVF/ICSI.

ESRHE Guideline for Endometriosis, 2013

IVF is the treatment alternative associated to the higher pregnancy rates in Endometriosis Infertility.

Our Experience:

Pregnancy rate in infertile patients after endoscopic resection of Deep-Infiltrating endometriosis

Pregnancy rate in infertile patients after resection of DIE (n=25)
- 20% Not pregnant
- 80% Pregnant

References
- Barnhart et al, Fertil Sterility 2002
- Schenken RS. J Reproductive Medicine 1998
- Stepniowska et al, RBM Online 2010
- Somigliana et al, Fert Sterility 2012
- Adamson, Endometriosis Fertility Index, Fertil & Steril 2009
- Darai et al, Fertility and Sterility 2011
- SART Registry 2000
- ESRHE Guideline for Endometriosis, 2013
Pain: How to be Successful in the Long Term in Patients with Endometriosis and Pain.
Or: Don’t Worship the Implant

John F. Steege, MD
University of North Carolina
Department of Obstetrics and Gynecology
Division of Advanced Laparoscopy and Pelvic Pain

I have no financial relationships to disclose.

Objectives
• Understand the neurologic overlaps among organ systems.
• Be aware of visceral cross-talk and central sensitisation.
• Know how to examine the patient with chronic pain.

The conventional wisdom
• The correlation between the amount of endometriosis present and the pain experienced is low, if present at all.
• Type of endometriosis may make a difference: infiltrative vs peritoneal implants
• Cases in which stage I disease is observed to progress to stage IV disease are very few.
• Not all women with endometriosis have pain.
• If pain increases despite reduction of lesions, then psychological factors may be in play.

Common practices
• Diagnosis made by history and physical exam.
  • Therapeutic trial of GnRH agonist.
  • If no improvement, then perform laparoscopy.
  • If pain recurs after laparoscopic treatment, then laparoscopy again.
  • If pain recurs despite repeat laparoscopy, then remove organs.
  • If pain recurs after organ removal, then refer to a pain clinic or for mental health care.
  • Other subspecialty consultations along the way, as indicated (gyn, urology, neurology, etc.)

How’s that workin’?
• Pain comes back 12-18 mos later
  • Change pills
    – Luteal
    – Add norethindrone
    – Add finasteride (or another inhibitor)
  • Re-laparoscopy: less disease than before
    – Have you ever seen stage I progress to stage IV?
    – Re-cook, re-wash, presacral neurectomy
  • Start taking things out
    – If pain lateralizes, take out a tube/ovary
    – Sweep at a young age.
The real disease

- Implant worship
- To be disease, I have to be able to see it.
- If I see it, it must be disease!

But what determines response to treatment?

- Bajaj: altered somatic pain thresholds in women with endometriosis
- As-Sanie: thumb pressure-pain thresholds correlate well with response to laparoscopic treatment of endometriosis.

Meaning?

- Assess the host, as well as the disease
- Set yourself up for success with a more complete assessment of pain from the start.
- Consider the implant as a possible trigger for pain, or possibly nothing at all.

Pain mechanisms in endometriosis

- Bleeding from implants: no
- Uterine contractility: probably (Mirena)
- Entrapment of nerves: maybe
- Ingrowth of nerves: Anaf, Berkley
- Prostaglandin production
- Inflammatory mediators: substance P, neurokinin A, calcitonin gene-related peptide, transient receptor potential vanilloid 1 (TRPV1)

Assessing the host

- You’re looking for contributing factors, not single alternative diagnoses.
- Pain is the disease.
- Organ systems do not exist in isolation.
  - “Multi-specialty evaluations” is an excuse for not doing a good evaluation yourself
  - Multiple organ endoscopies, in the absence of true signs of illness, are a waste of time.
  - The probability of independently contracting IBD, IBS, FM, CPS, and “osis” is very low.
- Psychological issues may develop during the course of illness, but are seldom the prime movers.
  - History of abuse
  - Depression

Cross-talk, central sensitization

- Cross-talk
  - Pelvic organ systems share innervation
  - Pain syndromes overlap with each other
  - Probabilities
- Central sensitization
  - Over time, central nervous system may become the pain generator
  - Less dependence on nociceptive signals from periphery
But how come laparoscopic surgery works so well?

• Severing of peritoneal nerves?
• Non-specific effect of surgery?
• Reduction of cognitive dissonance?

• Why is the endometriosis often less prominent at the second laparoscopy?

So what should the doctor do?

• Initial evaluation: History
  – Thorough history of pelvic pain
  – Menstrual sexual history
  – History of other disorders, especially pain disorders.
  – History of childhood diseases, frequent UTIs?
• Initial evaluation: physical exam
  – Low back, IT pains
  – Abdominal single digit, TPs, Carnett sign
  – Spleen single visceral exam
  – Muscles: pelvic floor, hips, referred to abdominal wall
• Patient education
  – The scope does not tell all.
  – Chronic pain can change the neurology

Initial steps

• Initial pharmacologic measures
  – Not a Lupron trial
  – Shutting off the HPO axis may alter pain sensitivity
• Laparoscopy
• Post-op medication
• Close observation

When the pain comes back

• Start over again
• Re-check muscles, etc.
• Re-review other organ systems
• Assess overall adjustment
• Are there other pain syndromes?
• Plan multiple treatments accordingly
• Pain is the illness
• Exam: look for visceral allodynia: vaginal cotton-tipped applicator
If you re-scope...

- Prepare the patient for the possibility that you won’t find much.
  - Don’t say that it’s the worst endometriosis you’ve ever seen.
- Prepare yourself for the possibility that you won’t find much.
  - Don’t say, “I want to do everything I know how to do.”
  - Be ready to say, “I think there may be many factors in your pain.”
- Have your other treatment suggestions ready to go:
  - PT for muscle elements
  - Psychotropics for pain
  - Muscle relaxants
  - Re-interpretation of pain episodes. (de-catastrophising)

And when it doesn’t work:

- Don’t say, “When in doubt, take it out.”
- Don’t say, “A chance to cut is a chance to cure.”
- Don’t say, “I want to do everything I know how to do” before referring
- Do not be afraid to say, “I don’t know.”

Summary

- Look beyond the implant
- Deal with the patient’s mythology about ‘osis.
- Deal with your own mythology about ‘osis.
- Understand the non-specific effect of surgery.
- Check the muscles, check the muscles, check the muscles.
- Understand other pain syndromes, visceral cross-talk, central sensitization.
- If several treatments for ‘osis don’t work, reconsider the diagnosis, as opposed to taking things out.
Adolescent Endometriosis and Early Diagnosis

Marc R. Laufer, M.D.
Chief of Gynecology
Children’s Hospital Boston
Center for Reproductive Medicine Brigham & Women’s Hospital
Director, Boston Center for Endometriosis
Harvard Medical School

Disclosure

I have no financial relationships to disclose.

Objectives

• At the conclusion of this presentation the participant will be able to:
  – identify common adolescent endometriosis lesions
  – Recommend treatment options for adolescents with endometriosis

15 year old with pelvic pain

• Pain for 6 months
• Worse with period
• Missing school
• Called your office with increased pain
• Sent to EW and found to have 6cm ovarian cyst
• Asked to follow up in Gyn
• Seen in Gyn 2 days after EW visit
• Asked to start OCP for dysmenorrhea and ovarian cyst suppression
• US 4 weeks later: normal
• Pain persists

Dysmenorrhea

• Accompanies 20 - 90% of adolescent menstrual cycles
• Dysmenorrhea that significantly interferes with function 1 - 3 days/month affects 5- 42% of adolescents
• More likely be primary than secondary in origin

Medical Management of Pelvic Pain/Dysmenorrhea

• Combined oral contraceptives (COC’s)
  – Numerous overall benefits
• Progestin-only OC’s may also be beneficial is special circumstances
• If there is a persistence of pain on COC and NSAIDS then we need to proceed with a diagnosis
How do we decide when it is no longer dysmenorrhea and further evaluation is required?

Don’t “normalize” symptoms

• Dysmenorrhea that fails to respond to conventional treatment is not a “normal” occurrence
• Women should not be led to believe that they simply have to endure pelvic pain because it is their lot in life to do so.

A young woman’s dreams

Costs of Endometriosis

• Yearly total (direct & indirect)
  – Europe: 30 billion Euros
  – US: 22 billion dollars

Data From the International Endometriosis Association


• Registry of 4000 women with endometriosis
• Most women see approximately 9 health care providers prior to diagnosis
• Most women have had symptoms that they associate with endometriosis since adolescence
  – 21% had severe pain under age 15
  – 17% age15-19
  – 12% age 20-24
  – 50% 24 or younger

Endometriosis: Etiologies

• Sampson’s theory: retrograde menstruation
• Hematogenous and/or lymphatic spread of endometrial tissue
• Metaplastic transformation
• Immune system abnormality to ectopic endometrium
• Environmental exposures [Dioxin]
• Genetic predisposition
**Endometriosis: Symptoms**

- None
- Pain: dysmenorrhea; localized pain; dyspareunia; noncyclic pain
- GI: constipation, diarrhea, hematochezia, melena
- GU: hematuria, dysuria, frequency, urgency
- Pelvic Mass/Cyst [not usually seen prior to age 22]
- Subfertility/Infertility: Stage I to Stage IV

**GI=gastrointestinal**
**GU=genitourinary**

**Endometriosis: Co-Occurrences**

- Interstitial Cystitis
- IBS
- Kidney/uteral stones
- Temporo-mandibular disorders
- Migraines
- Fibromyalgia
- Vulvodynia

**Adolescent Physical Exam**

- What is the goal?
  - Rule out:
    - Obstructive anomaly
    - Ovarian mass

- Bimanual
  - May not be possible
  - Q-tip test
  - Recto-abdominal
  - Unlikely findings
    - Uterosacral nodularity
    - Endometrioma

**Adolescent Endometriosis: Diagnosis**

- No diagnostic blood test
- No diagnostic imaging study
- History
- Physical Exam- A pelvic exam should not be barrier for evaluation [patency, ? Mass]
- Trial of NSAIDs & CHT
- Laparoscopy for diagnosis AND surgical management

**Incidence of Endometriosis in Adolescents With Pelvic Pain Diagnosed by Laparoscopy**

- 69% – Laufer (1997)*
- 97% – Laufer (2012)

*data from early ’90s, optics now better, ie higher rates

**Characteristics of Subjects With & Without Endometriosis**


<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with Endometriosis</th>
<th>N=32, Number (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting Symptoms</td>
<td></td>
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<tr>
<td>Acyclic and cyclic pain</td>
<td>20 (62.5)</td>
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<tr>
<td>Acyclic pain</td>
<td>9 (28.1)</td>
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<tr>
<td>Cyclic pain</td>
<td>3 (9.4)</td>
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<tr>
<td>Gastrointestinal pain</td>
<td>11 (34.4)</td>
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<tr>
<td>Urinary symptoms</td>
<td>4 (12.5)</td>
<td></td>
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<tr>
<td>Irregular menses</td>
<td>3 (9.4)</td>
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<tr>
<td>Vaginal discharge</td>
<td>2 (6.3)</td>
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</tr>
</tbody>
</table>
Data From the International Endometriosis Association

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- Most women see approximately 9 health care providers prior to diagnosis
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  - 17% age 15-19
  - 12% age 20-24
  - 50% 24 or younger

What’s the delay? A qualitative study of women’s experiences of reaching a diagnosis of endometriosis

- Significant delay in diagnosis [11.8y in US, 6.7 in UK]
- Diagnostic laparoscopy after failure of first line
- Women suffer at physical, emotional and social levels when they remain undiagnosed

Patients’ report on how endometriosis affects health, work, and daily life

- 108 patients in Puerto Pico
- Majority had symptoms starting 11-19 year of age
- Mean delay in diagnosis was 8.9 years
- Many patients consulted 5 or more physicians prior to diagnosis
- Endometriosis impairs health-related quality of life

There is no correlation between amount of disease and pain.

ASRM Staging Relates to Fertility Potential, Not Pain

Staging and Pain Are Unrelated

<table>
<thead>
<tr>
<th>Incidence:</th>
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</thead>
<tbody>
<tr>
<td>Stage I: 40%</td>
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<tr>
<td>Stage II: 24%</td>
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<tr>
<td>Stage III: 24%</td>
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<tr>
<td>Stage IV: 12%</td>
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</table>
Endometriosis in adolescents is a hidden, progressive and severe disease that deserves attention, not just compassion.


<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Subjects</th>
<th>Age Range</th>
<th>St I %</th>
<th>St II %</th>
<th>St III %</th>
<th>St IV %</th>
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<tbody>
<tr>
<td>Goldstein et al</td>
<td>1980</td>
<td>66</td>
<td>10-19</td>
<td>58</td>
<td>38</td>
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<td>1989</td>
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<td>Davies et al</td>
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<td>Bai et al</td>
<td>2002</td>
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<td>Ventolins et al</td>
<td>2005</td>
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<td>14</td>
<td>39</td>
<td>43</td>
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<tr>
<td>Staurovskas et al</td>
<td>2006</td>
<td>11</td>
<td>13-20</td>
<td>45*</td>
<td>55**</td>
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<td>Vignon et al</td>
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<td>Roman</td>
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<td>14-20</td>
<td>40</td>
<td>45</td>
<td>5</td>
<td>10</td>
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<td>Yang</td>
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<td>63</td>
<td>12-20</td>
<td>8</td>
<td>3</td>
<td>52</td>
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</table>

*~St 1&2, ~St 3&4

Endometriosis:
Types of Lesions and Pain

- Clear 76%
- Red 84%
- White 44%
- Black 22%
- Pain perception 1-27 mm from lesion


Immune Dysregulation and Inflammation in Endometriosis

Identification of Clear Lesions

• use of liquid medium to improve visualization
• improve magnification
• 3-dimensional effect


Surgical Approaches

• Laparoscopy [laparotomy is not a failure]
• Open laparoscopy vs. direct insertion
• Resection or Ablation
• Laser, scissors, harmonic scalpel, electrosurgery
• Hysterectomy
• Hysterectomy with bilateral oophorectomy

Surgical Excision vs Ablation


• Randomization at initial laparoscopy for CPP if Stage I or II diagnosed: ablation with cautery or excision
• 24 patients with 12 in each group with 6 month follow up
• Significant improvement in pain in both groups
• No difference in either group
• 1 patient in each group had worsening of symptoms

Clear lesions & destruction
Plaque lesions & destruction

Surgical Outcomes in Adults
Now we have published follow up in adolescents!

Medical Treatment for All Patients
- No surgical cure of endometriosis
- Treatment until childbearing is complete or fertility is no longer desired
- Limit the life-time surgical procedures
- Hysterectomy should not be a recommendation for an adolescent

Medical Treatment Options in Adults
- Estrogen/Progestin
  - Continuous [OCPs/Ring]
- Progestins
  - Depo-Provera
  - Aygestin [5-15mg/day]
- Danazol
- GnRH agonists with add-back
  - Aygestin [5mg]
  - PremPro [625/2.5]
  - Do Not Use OCPs for Add-back
- GnRH-antagonists with add-back
- Anti-estrogens or anti-progestins

Continuous Combination Hormonal Therapy
Monophasic progestin dominant pill-21
Disp# 4 packs [3 months]
Sig: 1 po q D without breaks or placebos for Rx of endometriosis

Progestins and Endometriosis
- +/- ovulation inhibition
- Decidualization
- Decreased menstrual flow
- Formulations
  - progestin only pill
  - Norethindrone acetate [5-15mg]
  - Depo-provera
**Use of norethindrone acetate alone for postoperative suppression of endometriosis symptoms**

- 194 patients with surgically confirmed endometriosis
- Median age 18.9 years [10.2 – 41.9]
- 92.2% had Stage I or II disease
- Pain 0-10 severity scale
- Bleeding 0-4
  - 0 = no bleeding, 1 = spotting, 2 = irregular bleeding once monthly, 3 = weekly bleeding, 4 = daily bleeding
- FDA approved dose: 5-15mg
- Self-titrate to amenorrhea and decreased pain

**Results**

- 55.2% had no SE
  - 16.1% wt gain
  - 9.9% acne
  - 8.9% mood swings
- 64.7% reported lower pain scores
- 58.1% reported reduced bleeding

**Bone Density in Adolescents Treated with a GnRH Agonist and Add-Back Therapy for Endometriosis**
DiVasta AD, Laufer MR, Gordon CC

- BMD at the hip normal in most adolescents with endometriosis receiving leuprolide and add-back therapy with norethindrone acetate
- 1/3 of subjects had clinically significant skeletal deficits (Z-score ≤ -1.0) at the spine
  - Greater than expected in normal population
  - Likely due to GnRH-a induced low-estrogen state
- Duration of treatment not associated with BMD at hip or spine

**Outcomes in Adolescents**

**The Effect of Standard Surgical-Medical Intervention on the Progression of Endometriosis**

- 90 patients age 12-24
- Laparoscopy for diagnosis & surgical treatment
- Medical treatment
  - Continuous E/P [91%]
  - LA + NA or Prempro [78%]
  - P only [12%]
- 2nd laparoscopy due to pain
- Trend towards disease progression not seen
- Standard surgical-medical management retards disease progression

**Necessity of Post-op medication?**

- 20 prospectively enrolled ages 12-19
  - Pre-op questionnaire
  - Laparoscopy with “complete excision of endometriosis”
  - F/u questionnaire @ 1-2 yr intervals (median f/u 23 months)
- No specific post surgical recommendation made to participants regarding hormonal therapy
  - May use for contraception or suppression “patient's choice”
Results

- 6/17 subjects OCP
  - Duration 10-22 months
- 1/17 subjects utilized GnRHa
  - Duration 6 months
- 8/17 subjects had recurrent pain and underwent repeat laparoscopy. No endometriosis appreciated [visually or histologically]

Conclusions

- Author’s conclusions
  - “Careful/complete excision of endometriosis” improves quality of life
  - Pain relief from surgery persist without medical therapy (up to 2 years)
- Problems:
  - Pain persisted in 50% of patient regardless of operative findings
  - 50% of patients required a 2nd operation within 2 years due to pain
  - Does not address fertility concerns

Adolescent Endometriosis Management

- Need for Diagnosis/surgery
  - ACOG: “After a comprehensive evaluation and an adequate trial of hormone therapy and NSAIDs, laparoscopy should be offered for diagnosing and treating presumed endometriosis”
- Surgical Treatment: excision/ablation of all visible lesions
  - Importance of adolescent lesions
- Since there is no cure for the disease, post-operative medical therapy until child bearing is complete

Endometriosis in adolescents is a hidden, progressive and severe disease that deserves attention, not just compassion


- Importance of early diagnosis
- Early intervention to avoid progression

Boston Center for Endometriosis

- Biorepository and Clinical Database
  - $3 million gift - J. Willard & Alice S. Marriott Foundation
  - Additional $1.5 million for research
- Development of a non-invasive diagnostic
- New treatments on the way to a cure
- Life long endometriosis data base from adolescence through adulthood [BCH & BWH]
  - Genetic predisposition, Environmental exposure, Diet, Long term follow up [% need for additional surgery, future fertility]
Current Research: Biorepository

- Collect blood, urine, saliva, fluid from the pelvic cavity, and tissue from adolescents and adult women with endometriosis
- Development of a non-invasive diagnostic
- New treatments on a way to a cure

Clinical Data Base

- Life long endometriosis data base
  - Genetic predisposition
  - "Fast track" evaluation and treatment
  - How should we manage the daughter of a woman with a history of infertility, Stage IV endometriosis, and no pelvic pain?
  - Associated diseases
  - Environmental exposure
  - Long term follow up [% need for additional surgery, future fertility]

The Importance of Awareness

- If adolescent endometriosis can be kept from progressing with surgical destruction followed by medical therapy
- And if early diagnosis can save a woman’s fertility and prevent extreme physical and emotional pain
- Need to improve awareness
  - www.endometriosisassn.org
  - www.youngwomenshealth.org
  - www.bostoncenterendometriosis.org

Education and Life Long Support

Educating Professionals
Conclusions

• Endometriosis does occur in adolescents
• Early diagnosis to decrease pain & progression
• Education and awareness is the key to decreasing pain, suffering and infertility

References

CULTURAL AND LINGUISTIC COMPETENCY

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

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

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

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

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

If you add staff to assist with LEP patients, confirm their translation skills, not just their language skills. A 2007 Northern California study from Sutter Health confirmed that being bilingual does not guarantee competence as a medical interpreter. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2078538.