Clinical and Research Aspects of Endometriosis

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Thursday, November 17, 2005
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Endometriosis Concepts
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Learning Objectives

Following the presentation “Research and Clinical Aspects of Endometriosis” participants should be able to:

• Define endometriosis and adenomyosis,
• Understand that the appearance of endometriosis changes with age,
• Describe the histological appearance of endometriosis and,
• List diagnostic methods for endometriosis.
The study of endometriosis is like nailing Jell-O to a tree.

- Donna Vogel, NIH 2002
Clinical and Research Aspects of Endometriosis

- Definition
- Theories and Observations
- Diagnosis
- Research

Considerations for treatment and treatment options will be expanded and discussed at a later date.
Concerns with Endometriosis

• Progression

Clear Vesicle →

Dark Scarred

Rectum
Age Associated Changes

- Water blister-like lesion turns red and begins to bleed. Then scar tissue occurs and blue dome cysts form. This occurs over 4 to 10 years. – Karnaky 1969

- The age distribution suggests progression from clear papules (21.5) to red lesions (26.3) to any white (28.3) to any black (28.4) to black only (31.9). The mean age difference from clear papules to black only is 10.4 years. – Redwine 1987

- The prevalence of deep endometriosis increases from 8.4% at age 20 to 19.7% at age 40. These changes are dominantly in type II and III infiltration. The overall prevalence was similar at 60% and 62%. – Koninckx 1992
Histological Diagnosis

Clear Vesicle → Hemosiderin

Clear Vesicle → Hemosiderin
Histological Diagnosis

• Red Fibromuscular Zone → Glands and Stroma

• Fibro-Muscular Metaplasia

Fibro-Muscular Zone → Glands and Stroma

Glands and Stroma
Histological Diagnosis

- Fibro-Muscular Zone
- Glands and Stroma
- Fibro-Muscular Metaplasia
- Collagen
- Muscle
- H&E Stain
- Trichrome Stain
Histological Diagnosis

- ST lesion
- Glands
- Stroma
- Fibro-Muscular Metaplasia
- Old Blood Residual
Histological Diagnosis

- Glands
- Stroma
- Fibro-Muscular Metaplasia
- Old Blood Residual
• Endometriosis has been found in the lungs, skin, liver, pancreas, spine and brain.
  • Bergqvist 1990 - 2006
But,

Endometriosis is not always progressive.

- **Endometriosis is where you look.**
  400th vs. 200th Case
  - Fallon 1950

- **Endometriosis might be found in**
  100% of all 40 year old women.
  - Scott, TeLinde and Wharton 1953

- **Endometriosis is not a disease,**
  all women have endometriosis.
  - Evers 1994
Clinical and Research Aspects of Endometriosis

• **Definition**
• **Theories and Observations**
• **Diagnosis**
• **Research**
What is Endometriosis?

- The **endometrium** is composed of endometrial glands, stroma and other elements.
- **Endometriosis** is the presence of endometrial tissue outside of the uterus.
- **Adenomyosis** is the presence of endometrial tissue within the muscle wall of the uterus.
What is Endometriosis?

- Grade 1: **Possible residua** of resorbed endometriosis, such as hemosiderin, calcium, nerve, blood vessels and/or smooth muscle.
- Grade 2: **Consistent with endometriosis**, such as glands or stroma.
- Grade 3: **Definite endometriosis** with glands and stroma.
- Grade 4 (Gross): **Grade 3 with a gross structure** conveying an organoid pattern, such as glandular-stromal layer overlying well-developed smooth muscle layer.

Endometrium
Endometriosis

Fibromuscular Metaplasia

Glands

Stroma
Adenomyosis
Adenomyosis
Clinical and Research Aspects of Endometriosis

- Definition
- Theories and Observations
- Diagnosis
- Research
Theories and Observations

• **Retrograde Menstruation and Implantation**
  – Sampson 1927
  • Structurally normal pelvis
  • Compromised cell-mediated immunity
  • Exposure to environmental toxins
  • Outlet obstruction due to congenital anomalies

• **Antegrade menstruation** to a site of vulvar trauma

• **Surgical Transplantation**
  • Episiotomy
  • Cesarean section
  • Abdominal or vaginal hysterotomy
  • Surgical correction of uterine anomalies
Theories and Observations

- **Mullerian Rests**: The theory of embryonic Mullerian rests is predicated on the assumption that cell rests of paramesonephric (Mullerian) origin occur in the embryonic pelvis and are stimulated by ovarian steroids at menarche. – Von Recklinghausen 1896, Russell 1899

- **Coelomic Metaplasia**: The coelomic metaplasia theory describes formation of a secondary Mullerian system and endometriosis within the coelomic cavity. The coelom is the central body cavity that contains major organs. – Meyer 1919

- **Induction Theory**: The induction theory suggests that coelomic metaplasia occurs because menstrual endometrium contains substances that induce peritoneum to form endometriosis – Fujii 1991

- **Lymphatic Spread**: Endometriosis is found in lymphatics and lymph nodes. The umbilicus may receive lymphatic drainage from the pelvis. – Halban 1924, Javert 1952

- **Hematogenous metastases** may be the source of distant endometriosis to the lungs, skin, liver, pancreas, spine or brain. – Sampson 1925, Javert 1952, Bergqvist 1990/2006
Theories and Observations

• **Genetics:** Endometriosis is probably inherited as a complex genetic trait, since among first-degree relatives of affected women, the prevalence of endometriosis, adenomyosis, or both is six to nine times higher than in the normal population.

Theories and Observations

- **Teenagers – Superficial Red Lesions**
  - Increased prostaglandin synthesis – Vernon 1986
  - Diarrhea and bowel symptoms – Davis 1993

- **Age 32 – Dark Scarred Lesions**
  - 4 to 20 years – Karnaky 1969, Redwine 1987, Koninckx 1992
  - Focal Pain and Tenderness
Theories and Observations

- Steroid Receptors and Hormones
- Growth Factors and Cytokines
- Sympathetic Nervous System
- Immunocompetent Cells
- Embryonic Development
- Eutopic Endometrium
- Basalis Layer
- Angiogenesis

- Apoptosis
- Extracellular Matrix
- Adhesions Molecules
- Cellular Analysis
- Molecular Analysis
- Glucocorticoids

- 848 of the 1,492 references in “Endometriosis in Clinical Practice”
  David Olive, 2005
Theories and Observations

Balanced System
- Buffington 2004

Overactive SNS
Theories and Observations

- Buffington 2004
Clinical and Research Aspects of Endometriosis

- Definition
- Theories and Observations
- Diagnosis
- Research
What is Endometriosis?

- Histology
- Laparoscopic Appearance
- Associated Symptoms
- Associated Signs
Diagnostic Standard

• Do we have a gold-standard?

• Is it useful?
  • Does it predict the therapy to use?
  • Does it predict a response to therapy?
  • To make a difference, it must make a difference.
    • Carl Levinson, UCSF
Diagnostic Standard

- History and Physical
- Markers
- Visual Identification
- Histopathologic Confirmation
Clinical Diagnosis

• History
  • PPV of 78% and 87%
  • Sensitivity – 50%
  • Specificity - 95%
    • Kirtland Endo IX 2005

• Pelvic Exam
  • Sensitivity - 36-92%
  • Specificity - 32-97%
    • Spczynski Semin Reprod Med 2003
Pelvic Pain Algorithm

Adapted from ACOG Committee Opinion Number 310, Endometriosis in Adolescents, Number 310 April 2005

If Persistent Pain

- **History**
- **Physical Exam**
- **Lab Tests (Blood, Urine)**
- **Consider Radiologic Imaging**
- **Pain Diary**

**NSAIDs and/or Cyclic BCPs**

- **Empiric GnRH Agonist** *(if >18 Years)*

If No Improvement

- **Laparoscopy**
- **Dx is Endometriosis**

- **Endometriosis Identified and Surgically Managed**

- **Medical Therapy Until Fertility and Child Bearing Complete**

If Endometriosis Not Identified

- **GI or Urologic Evaluation**
- **Pain Management Service**

Not Always. It can be:
- **Primary Dysmenorrhea**
- **Myomata**
- **Adenomyosis**
- **Migraines**
- **IBS**
Empirical Depo-Leuprolide

- 88 Women
- Patient Selection Based on History
- 71 (81%) had Endometriosis
  - Ling FW, Obstet Gynecol 93:51, 1999
Empirical Depo-Leuprolide

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Depo-Leuprolide</th>
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<tbody>
<tr>
<td></td>
<td>Pain Relief</td>
<td>No Relief</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>15 (39%)</td>
<td>23 (61%)</td>
</tr>
<tr>
<td>No Endometriosis</td>
<td>1 (20%)</td>
<td>5 (80%)</td>
</tr>
</tbody>
</table>

Ling FW, Obstet Gynecol 93:51, 1999
Imaging

• Transvaginal Ultrasound
  • Sensitivity 57-92%; Specificity 91 – 99%
  • Best data in studies of ovarian endometriomas

• MRI
  • Sensitivity 11-91%; Specificity 60-98%
  • Best data in studies of ovarian and deep rectovaginal endometriomas

CA-125

- Sensitivity 24-94%
- Specificity 83-93%
- Performance on late stage disease is good, but detection of early stage disease is generally much lower
IL-6 and TNF-alpha

- Sensitivity 90-100%
- Specificity 67-89%
- Possibly useful in the detection of early stage disease.
- Further study is needed.
Ease of Confirmation

- Endometriosis is difficult to confirm.
  - Expectation of Appearance
  - Biopsy Techniques
  - Signal to Noise Ratio
  - Marking specimen
  - Notations on Pathology Request
- 400\textsuperscript{th} vs. 200\textsuperscript{th} Case – Fallon 1950
- Endometriosis is missed at surgery.
Signal to Noise Ratio

Clear Vesicle →

← Hemosiderin

← Noise / “Margin” Excisional Zone →

Glands and Stroma

Fibro-Muscular Metaplasia

← Noise / “Margin” Excisional Zone →
## Confirmation – 495 Cases

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Endo Patients</td>
<td>97</td>
<td>91</td>
<td>91</td>
<td>97</td>
<td>119</td>
</tr>
<tr>
<td>Patients with</td>
<td>13</td>
<td>34</td>
<td>65</td>
<td>88</td>
<td>119</td>
</tr>
<tr>
<td>Tissue Excised</td>
<td><strong>13%</strong></td>
<td>37%</td>
<td>71%</td>
<td>91%</td>
<td><strong>97%</strong></td>
</tr>
<tr>
<td>Positive for Endo</td>
<td>8</td>
<td>17</td>
<td>59</td>
<td>84</td>
<td>116</td>
</tr>
<tr>
<td>All Patients</td>
<td>8%</td>
<td>19%</td>
<td>65%</td>
<td><strong>87%</strong></td>
<td>97%</td>
</tr>
<tr>
<td>If Excised</td>
<td><strong>62%</strong></td>
<td><strong>50%</strong></td>
<td>91%</td>
<td>93%</td>
<td><strong>97%</strong></td>
</tr>
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</table>

Martin, 1987
## Range of Confirmation

<table>
<thead>
<tr>
<th>Cases per Physician</th>
<th>≤ 5</th>
<th>6-11</th>
<th>12-26</th>
<th>127</th>
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</thead>
<tbody>
<tr>
<td>Scott 1952</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Martin 1990</td>
<td>48%</td>
<td>57%</td>
<td>76%</td>
<td>99%</td>
</tr>
<tr>
<td>Pardanani 1988</td>
<td>-</td>
<td>65%</td>
<td>55%</td>
<td>-</td>
</tr>
<tr>
<td>Walters 2001</td>
<td>-</td>
<td>45%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
## Confirmation of Endometriosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
<th>+/-</th>
<th>-/+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott 1952</td>
<td>516</td>
<td>64%</td>
<td>31%</td>
</tr>
<tr>
<td>Martin 1990</td>
<td>489</td>
<td>70%</td>
<td>29%</td>
</tr>
<tr>
<td>Pardanani 1988</td>
<td>91</td>
<td>59%</td>
<td>-</td>
</tr>
<tr>
<td>Walters 2001</td>
<td>44</td>
<td>45%</td>
<td>-</td>
</tr>
</tbody>
</table>
Histology Based Response

- One Study
- Damario and Rock 1994
Uterosacral Endometriosis

Pain Relief

• 8 of 8 (100%) with endometriosis.
• 6 of 8 (75%) if histology negative.
  • Damario and Rock 1994
Diagnostic Standard

• Professional Society Guidelines Support Visualization
  
  • ESHRE 2005 guideline states: “for a definitive diagnosis of endometriosis, visual inspection of the pelvis at laparoscopy is the ‘gold standard’…”

  • 2005 - ACOG Committee Opinion 310, 2005, *Endometriosis in Adolescents* indicates that laparoscopy with “visualization or biopsy” is needed to diagnose endometriosis.
Tissue Diagnosis

- A major clinical purpose of biopsy is to exclude other pathology.
- When the histology is uncertain (hemosiderin, scar, smooth muscle, no pathologic findings), the original clinical diagnosis is kept.
- In research treatment protocols, biopsy are often avoided as they may modify the behavior of the process.
Other Pathology

Psammoma Bodies
Endosalpingiosis
Low Malignant Potential Tumor
Cancer
Other Pathology
Deep Endometriosis
Superficial or Deep
Superficial or Deep
Superficial or Deep

2 mm

5 mm
Retroperitoneal Endometriosis
Retroperitoneal Endometriosis
Ring Forceps Test

• Forceps are seen with partial cul-de-sac obliteration (PCDSO)

• The forceps are not seen with complete cul-de-sac obliteration (CCDSO)

  • Reich 1991
Rectovaginal Endometriosis

- RV Pouch is to the middle third of the vagina in 93% of women.
  - Kuhn 1982
Ring Forceps Test
Ring Forceps Test
Ring Forceps Test
Retroperitoneal Endometriosis
Adamyan Classification

Stage I

Stage III
Rectovaginal Pouch Obliteration
Retrocervical Endometriosis

- Rectovaginal endometriosis is more rectocervical than rectovaginal.
  - Adamyan, 1993
  - Martin 2001, 2005
  - Swoboda 2004
Retrocervical Endometriosis

Futh 1903

Sampson 1918
Retrocervical Endometriosis

- Involvement of the mid-vagina is rare.
- 1 in 80 to 1 in 300 bowel cases.
  - Swoboda 2005
Clinical and Research Aspects of Endometriosis

- Definition
- Theories and Observations
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- Research
### Degree of Involvement

<table>
<thead>
<tr>
<th>Referral Practice*</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of Endometriosis</td>
<td>25%</td>
<td>70%</td>
</tr>
<tr>
<td>Deep Endometriosis</td>
<td>5%</td>
<td>53%</td>
</tr>
<tr>
<td>Bowel Endometriosis</td>
<td>6%</td>
<td>12%</td>
</tr>
<tr>
<td>Mid-Vaginal Endometriosis</td>
<td>0.1%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Martin 1997, 2005

*Does referral practice = EBM?
# Irritable Bowel Syndrome

## Spectrum of Clinical Features Among Patients with IBS

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated prevalence</td>
<td>70%</td>
<td>25%</td>
<td>5%</td>
</tr>
<tr>
<td>Practice type</td>
<td>Primary</td>
<td>Specialty</td>
<td>Referral</td>
</tr>
<tr>
<td>Correlation with gut physiology</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Symptoms constant</td>
<td>0</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Psychosocial difficulties</td>
<td>0</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Health care use</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

0, generally absent; +, mild; ++, moderate; ++++, marked.

Diagnostic Criteria

Chronic Pelvic Pain

- Moderate to severe chronic pelvic pain, pain was unrelated to menstruation, pain incompletely relieved with NSAIDs, no gu or gi disease, etc.
- 71 (81%) of 88 women had endometriosis.
  - Ling FW, Obstet Gynecol 93:51, 1999

Dysmenorrhea

- Endometriosis is more associated with cyclic pain (dysmenorrhea) than with chronic pelvic pain.
Dysmenorrhea

- **29% to 44% in a family practice setting.**

- **16% to 80% in a literature review**
## Degree of Involvement

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Endometriosis <em>(D’Hooghe, Evers)</em></td>
<td>76%</td>
<td>100%</td>
</tr>
<tr>
<td>Symptomatic Endometriosis</td>
<td>16%</td>
<td>80%</td>
</tr>
<tr>
<td>Surgical Dx of Endometriosis</td>
<td>0.9%</td>
<td>8%</td>
</tr>
<tr>
<td>Deep Endometriosis</td>
<td>0.03%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Bowel Endometriosis</td>
<td>0.01%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Mid-Vaginal Endometriosis</td>
<td>0.0002%</td>
<td>0.003%</td>
</tr>
</tbody>
</table>

Martin 1997, 2005
Initial Approach to Endometriosis

• The initial care of endometriosis associated pain in a primary setting is NSAIDs and/or hormonal suppression.
• Surgery is reasonable at an intermediate level.
• Deep surgery and comprehensive pain treatment may be limited to less than 5% of patients with endometriosis – but those are the patients in the literature. (= EBM?)
Difficulties in Clinical Care and Research

- Markers
- Kappa Values
- Pimple Model
Difficulties in Clinical Care and Research

• Markers are not always reproducible.
  • Immunological Markers
  • Surgical Appearance
  • History and Physical
  • Mapping
    • Pain by Patients
    • Tenderness by Physicians
Difficulties in Clinical Care and Research

- Kappa Values
  - IM Injection
  - Oral, Nasal or Transdermal Medication
    - Patient Compliance
- Surgery
  - Variable Training and Experience
Clinical and Research Aspects of Endometriosis

- **Pimple Model**
  - We can see ugly. We do not see focal pain.
  - Endometriosis may be transient and self-limited in many women.
  - The appearance of endometriosis may not directly correlate with symptoms.
Conclusions

• Endometriosis may exist as a transient abnormality in up to 100% of women.
  • Pimple Model.

• Endometriosis progresses to mid-vagina involvement in no more than 0.003%.
  • Endometriosis is not commonly a deeply invasive disease.
Conclusions

• Endometriosis may be a disease if there is:
  • Pain
  • Infertility
  • Mass
  • Organ Obstruction
  • Progression
Conclusions

• Biopsy for Histology
  • The best use of biopsy may be to exclude other pathology.
  • Histology would be a good research standard if it did not interfere with data interpretation.
Links

Updated 11/20/18

• www.danmartinmd.com
• www.danmartinmd.com/files/lae1988
• www.danmartinmd.com/files/coloratlas1990
• www.danmartinmd.com/files/lae1991