Endometriosis
A new look at an old disease

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My Background

- Northwestern University Med School 1990
- Residency Bethesda Naval Hospital 1994
- Military Service Guam / Pensacola FL 1994-98
- Private Practice Kailua HI 1998-2006
  - Urogyn and general GYN
- Worked with Dr. David Redwine 2006-2008
  - Laparoscopic Endometriosis Excision
- Franciscan Medical Group 2008-current
  - Over 600 robotic cases
  - Specializing in Endometriosis and Urogynecology
Incidence

- 6-10% of Reproductive Aged Women
- 20-50% in Infertile Women
- 71-87% of Women with Pelvic Pain
Cardinal symptoms of endometriosis

**Peritoneal disease:** (most common in culdesac, uterosacral ligaments, broad ligaments)

- Cyclical pelvic pain (either central or lateralizing)
- Deep dyspareunia
- Painful bowel movements only during menstruation
- Pre-menstrual sharp, shooting, knifelike pain
- Dysmenorrhea (can also be from uterine causes)

**Intestinal Endometriosis:**

- Rectal pain with each bowel movement throughout the month
- Nausea, especially closer to menses
- Bloating, distension, early satiety
Pelvic Pain Not Likely to be Directly Related to Endo

- Bladder Pain (IC)
- Tailbone Pain (Levator Spasm)
- Electric Shocks in Vagina (Pudendal Neuralgia)
- Pain from spasms in all 3 of the following: Psoas, Obturator, and Piriformis muscles (Usually indicates a musculoskeletal cause)
Theories of Origin
Sampson’s Theory

• **Reflux Menstruation**
  - Happens in 85% of women

• **BUT…**
  - Only 15% of women get endo
  - Endo follows reproducible patterns
  - Women don’t develop disease in more places as they get older
  - Should result in endometriosis identical to endometrium (autotransplant)
  - Gene expression different in endometriosis than in endometrium

If you believe in Sampson’s theory, it means that Endometriosis can never be cured!
Metaplasia Theory

- Integrates with undisputed facts
  - Location of endometriosis lesions
  - Static nature of disease (grows deeper, not wider)
  - Occurrence outside abdomen (brain, lung, prostate)
  - Endo found in infant, premenarchal girls
  - Genes found in peritoneum of women with endo, absent in normal patients
  - Ability of peritoneum to “morph” into tissues resembling other areas of the reproductive tract

- May be pre-programmed during embryological development or form later in life under influence of estrogen

Allows for the ability to cure endometriosis!
Peritoneal Metaplasia

- “Secondary Mullerian system”
  - Innate ability of peritoneal cells to change into cells resembling all parts of the female reproductive tract
- Endosalpingiosis
- Endocervicosis
- Leiomyomatosis peritonealis disseminata
- Primary Peritoneal Carcinoma

Lauchlan, 1972

Peritoneal Metaplasia

- Integrates with undisputed facts:
  - Ability of peritoneum to “morph” into mullerian type tissues
  - Location of endometriosis lesions (uterosacrals, CDS, ovarian fossae
    most common)
  - Static nature of disease (grows deeper, not wider)
  - Occurrence outside abdomen (brain, lung, prostate)
  - Initial transformation has been visualized in ovaries
  - Endo found in infant, premenarchal girls
  - Genes found in peritoneum of women with endo, absent in
    normal patients
Normal appearing peritoneal cells in women with endometriosis contain activated genes required for the formation of the uterus and endometrium. (WNT7A, PAX8)

These genes are absent in women without endometriosis.

Enables development of endometriosis and other mullerian type tissue from peritoneum.
Initial transformation from normal ovarian tissue to endometriosis has been visualized.

110 cases of ovarian endometriosis, 34 showed IE

Zheng, et al Int J Gynecol Pathol 2005
Endometriosis has been identified in human fetuses

- Autopsy study of 36 female fetuses from 14 weeks to term
- Stained for CA-125 and estrogen receptors

- 4 of 36 (11%) had glands and stroma outside the uterine cavity
  - Culdesac, rectovaginal septum, rectum, posterior myometrium
Genetic influences

- A study of nearly 250 families with 3 or more affected women revealed genes on chromosome 7p that indicate a high probability for Mendelian inheritance (similar to genes for eye color, hair color, etc).

- Specific genes isolated in peritoneum of women with endo, absent in those without endo.

- Endometriosis cells express different genes than native endometrial cells from the same patients.
  - Proves that endometriosis is not an autotransplant.
Diagnosis

- **History**
- **Detailed pelvic exam**
  - Nodularity of culdesac, uterosacral
  - May also have levator spasm; uterine or bladder tenderness
  - Need to differentiate culdesac and uterosacral tenderness from uterine, bladder, levator tenderness
- **Imaging**
  - Only able to show DIE lesions, Endometriomas
  - Ultrasound great for rectal and low sigmoid lesions
  - MRI
  - Virtual Colonoscopy
Diagnosis

- Laparoscopy - gold standard
  Need Histology - visual appearance is unreliable
  PPV 45%, NPV 99%, Sensitivity 97%, Specificity 77%

Adenomyosis
Obliterated culdesac
Post Hysterectomy Rectovaginal Nodule
Adenomyoma and rectal nodule
Sigmoid Nodule
Terminal Ileum
Appendix
Treatment

- **Medical**
  - OCP
  - Progestins
  - GnRH agonists
  - Aromatase Inhibitors
  - Mirena IUD

- **Surgical**
  - Ablational Techniques
  - Excision
Harada, et al
- Double blind, randomized, placebo controlled
- Dysmenorrhea, endometrioma volume reductions significant
- Non-menstrual pelvic pain decreased, ns

Vercellini, et al
- Post excision use of OCPs and endometrioma recurrence
- Incidence of endometriomas at 36 mos postop:
  - 6% in OCP users, 49% in non-users

Seracchioli, et al
- Randomized, prospective trial of cyclical, continuous, or no OCPs after excision of endometriomas
- 14.7% (cycl), 8.2% (cont), 29% (none) recurrence at 24 mos
Medical management -
GnRH agonists

- Waller and Shaw, 1993
  - 130 pts with laparoscopically proven endo
    - 67% visual diagnosis only, 32% histologic
    - 61 women had pain only, 69 had infertility
  - Treated for 6 months with Buserelin, Naferelin, Goserelin (not leuprolide)
  - Most had second look laparoscopy at 6 months (while suppressed), then followed every 6 months for 2 years
  - Recurrences were either “documented” or “undocumented”
    - Documented: visual lesions on laparoscopy or histological disease at laparotomy
    - Undocumented: Recurrence of pain, laparotomy with negative histology

Waller and Shaw, Fertil Steril 1993;59:511-5
## Waller and Shaw Results

<table>
<thead>
<tr>
<th>Stage</th>
<th>Recurrence at 1 year</th>
<th>2 years</th>
<th>3 years</th>
<th>4 years</th>
<th>5 years</th>
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<tbody>
<tr>
<td>I</td>
<td>7%</td>
<td>19%</td>
<td>27%</td>
<td>27%</td>
<td>37%</td>
</tr>
<tr>
<td>II</td>
<td>15%</td>
<td>31%</td>
<td>43%</td>
<td>64%</td>
<td>74%</td>
</tr>
<tr>
<td>III</td>
<td>9%</td>
<td>29%</td>
<td>38%</td>
<td>48%</td>
<td>48%</td>
</tr>
<tr>
<td>IV</td>
<td>17%</td>
<td>43%</td>
<td>62%</td>
<td>75%</td>
<td>75%</td>
</tr>
</tbody>
</table>
More GnRH agonist data

- Dlugi, et al
  - Phase III study of lupron 3.75mg monthly
  - 63 patients enrolled, 32 in treatment group
  - 3 dropped out of tx group (2 increasing pain, 1 severe SE)
  - Evaluated dysmenorrhea, pelvic pain, dyspareunia, and pelvic tenderness
  - Best outcomes were in dysmenorrhea group (because menses were suppressed)
  - No significant difference in dyspareunia, small improvement in pelvic pain and tenderness

- 23/29 had significant decrease in BMD
- 57% had pain return by 6 months post treatment

Fertil Steril 54:419, 1990
Endometriosis: An overview of Cochrane Reviews - 2014

- **Pain:**
  - Low quality evidence of benefit of GnRH-a vs placebo
  - Moderate quality evidence of LNG-IUD vs expectant mgt
  - Very low quality evidence of Danazol vs placebo
  - NO DIFFERENCE between GnRH-a and OCPs or progestins
  - NSAIDS - inconclusive
  - Moderate quality evidence of benefit of laparoscopic surgery

- **Infertility:**
  - Moderate quality evidence that live births and pregnancy rates were higher after surgery
  - No evidence that postop medical therapy improves fertility
Surgical Approaches to Endo

- **Ablative techniques (laser, cautery)**
  - Burns top 1-2mm of tissue
  - Can’t reach deeply infiltrating disease
  - Doesn’t work for bowel disease, endo over ureters or vessels

- **Excision**
  - Removes all visible disease without removing reproductive organs
  - Allows for removal of endo over ureter, on bowel, diaphragm, etc.
- Very few studies
- Short term studies (6 mo f/u) show equivalent results with excision for MILD disease  
  Wright, et al Fertil Steril 2005
- 1 study with 6 year f/u of laser ablation in stage 1 and 2 disease 
  – 74% chance of pain recurrence at an avg of 20 mos 
  Jones, et al JSLS 2001
- No studies of ablation for stage IV endo
Surgical treatment of endometriosis: a prospective randomized double-blinded trial comparing excision and ablation

Their conclusion
- no significant difference in postoperative pain at 12 months

- 54 pts in excision group, 49 ablation
- 21 and 25 patients lost to followup - not enough statistical power
- 53% of excision group and 22% of ablation group had deeply infiltrating disease
- No stage IV patients in ablation group, 4 in excision group
- Residents performed the surgeries

Heaney, et al Fertil Steril 2010
## Reduction in VAS score by 12 months after operation.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Excision group mean (SD)</th>
<th>Ablation group mean (SD)</th>
<th>T-test P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall pain</td>
<td>2.9 (3.4)</td>
<td>2.9 (2.9)</td>
<td>.93</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>2.6 (3.5)</td>
<td>2.7 (2.7)</td>
<td>.94</td>
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<tr>
<td>Period pain</td>
<td>2.4 (3.9)</td>
<td>2.0 (3.9)</td>
<td>.69</td>
</tr>
<tr>
<td>Back pain</td>
<td>1.6 (3.9)</td>
<td>1.1 (2.9)</td>
<td>.49&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Rectal pain</td>
<td>1.4 (3.7)</td>
<td>0.5 (2.7)</td>
<td>.22</td>
</tr>
<tr>
<td>Thigh pain</td>
<td>0.9 (2.9)</td>
<td>0.4 (3.0)</td>
<td>.46</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.4 (3.1)</td>
<td>2.0 (3.7)</td>
<td>.60</td>
</tr>
<tr>
<td>Defecation pain</td>
<td>1.8 (3.5)</td>
<td>0.7 (3.1)</td>
<td>.16</td>
</tr>
<tr>
<td>Voiding pain</td>
<td>0.4 (2.3)</td>
<td>0.6 (2.7)</td>
<td>.70</td>
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<tr>
<td>Nausea</td>
<td>1.7 (2.7)</td>
<td>0.6 (3.6)</td>
<td>.13</td>
</tr>
<tr>
<td>Abdominal bloating</td>
<td>2.4 (3.4)</td>
<td>1.5 (2.8)</td>
<td>.21</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.1 (2.4)</td>
<td>0.9 (2.3)</td>
<td>.60</td>
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<tr>
<td>Dyspareunia</td>
<td>3.1 (4.1)</td>
<td>1.8 (4.1)</td>
<td>.17</td>
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</table>
At 5 years

<table>
<thead>
<tr>
<th>Factor</th>
<th>Excision Group Mean (SD)</th>
<th>Ablation Group Mean (SD)</th>
<th>T-test p value</th>
<th>Multivariate p value</th>
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<tbody>
<tr>
<td>Overall pain</td>
<td>2.9 (3.4)</td>
<td>2.9 (2.9)</td>
<td>.66</td>
<td>.86</td>
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<tr>
<td>Pelvic pain</td>
<td>2.6 (3.5)</td>
<td>2.7 (2.7)</td>
<td>.90</td>
<td>.43</td>
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<tr>
<td>Period pain</td>
<td>2.4 (3.9)</td>
<td>2.0 (3.9)</td>
<td>.46</td>
<td>.38</td>
</tr>
<tr>
<td>Back pain</td>
<td>1.6 (3.9)</td>
<td>1.1 (2.9)</td>
<td>.98</td>
<td>.87</td>
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<tr>
<td>Rectal pain</td>
<td>1.4 (3.7)</td>
<td>0.5 (2.7)</td>
<td>.51</td>
<td>.89</td>
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<tr>
<td>Thigh pain</td>
<td>0.9 (2.9)</td>
<td>0.4 (3.0)</td>
<td>.30</td>
<td>.32</td>
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<tr>
<td>Abdominal pain</td>
<td>2.4 (3.1)</td>
<td>2.0 (3.7)</td>
<td>.35</td>
<td>.03</td>
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<tr>
<td>Defecation pain</td>
<td>1.8 (3.5)</td>
<td>0.7 (3.1)</td>
<td>.85</td>
<td>.83</td>
</tr>
<tr>
<td>Voiding pain</td>
<td>0.4 (2.3)</td>
<td>0.6 (2.7)</td>
<td>.72</td>
<td>1.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.7 (2.7)</td>
<td>0.6 (3.6)</td>
<td>.65</td>
<td>.72</td>
</tr>
<tr>
<td>Abdominal bloating</td>
<td>2.4 (3.4)</td>
<td>1.5 (2.8)</td>
<td>.80</td>
<td>.69</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.1 (2.4)</td>
<td>0.9 (2.3)</td>
<td>.95</td>
<td>.74</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>3.1 (4.1)</td>
<td>1.8 (4.1)</td>
<td>.04</td>
<td>.007</td>
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</table>
Conservative Excision of Endometriosis

- Surgical removal of all disease, leaving normal reproductive organs in situ
- No need to castrate women in their 20s, 30s, or early 40s
- Allows for treatment of deeply infiltrating endometriosis, as well as lesions overlying the ureter, on the bowel or in the wall of the bladder
Published *CURE* rates after excision

As judged among reoperated patients:

- **66%** cured by laparotomy excision

- **57%** cured by laparoscopy excision*
  Redwine DB. *Fertil Steril* 1991; 56:628-34

- **57%** cured by laparoscopy excision
  Varol et al. *JAAGL* 2003:10;182-9
Recurrence: Amount of new disease after excision, quarterly

Mean number of pelvic areas involved at reoperation
IBS or something more?
A closer look at intestinal endometriosis

Linda Pai MD
Franciscan Surgical Associates
Gig Harbor, WA
Early Descriptions

Lockyer 1913

Fig. 1.
Growth in recto-uterine and recto-vaginal septa.
Early Descriptions

TS Cullen
1914-1920
Early Descriptions

JA Sampson
1921
Frequency by Location

Rectum/rectosigmoid: 65.7%
Sigmoid: 17.4%
Appendix: 6.4%
Cecum/ileocecal jct: 4.1%
Small bowel: 4.7%

1 area involved in 71%
2 areas involved in 21%
3 areas involved in 5%
>3 areas involved in 3%
Symptoms

- Diarrhea
- Constipation
- Tenesmus
- Dyschezia
- Painful bowel movements all month long
- Nausea/vomiting
- Decrease in caliber of stool (pencil thin)
**Diagnosis**

- **History**
- **Detailed pelvic exam**
  - Nodularity of culdesac, uterosacral nodes
  - Point tenderness of nodules
  - May also have levator spasm; uterine or bladder tenderness
- **Laparoscopy - gold standard**
- **Imaging**
  - Only able to show DIE lesions
  - U/S, MRI, CT Colonography best imaging modalities
- **Colonoscopy**
  - Only able to see full thickness lesions
  - 6% of bowel endo invades mucosa
**Imaging Studies**

- **Savelli, et al**
  - Compared transvaginal ultrasound with dual contrast BE

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Dx Accuracy</th>
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<tr>
<td>TVUS</td>
<td>85%</td>
<td>100%</td>
<td>100%</td>
<td>17%</td>
<td>85.5%</td>
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<tr>
<td>DCBE</td>
<td>36%</td>
<td>100%</td>
<td>100%</td>
<td>4%</td>
<td>38%</td>
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*Ultrasound Obstet Gynecol 2011;38:466-471*
• Jeong, et al

- Compared CT colonography with MRI

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Dx Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT Colonography</td>
<td>96%</td>
<td>48%</td>
<td>78%</td>
</tr>
<tr>
<td>MRI</td>
<td>94%</td>
<td>37.5%</td>
<td>69%</td>
</tr>
</tbody>
</table>

*J Comput Assist Tomogr 2013;37:809-814*
Ultrasound

Best for rectal/rectosigmoid lesions
Sensitivity/specificity: 91/98%
MRI

- No randomized studies comparing MRI with U/S or CT
- Better at visualizing lesions above the culdesac
- Diagnostic accuracy 96% in study of 28 women with bowel endo, preop MRI compared with histopathology and surgical findings
Virtual Colonoscopy

VC images courtesy of Dr. Johan van der Wat
Virtual Colonoscopy

3D transparent view Stricture
Virtual Colonoscopy

Fly Through view
Stricture
Management

• Medical therapy shown by multiple studies not to be effective for DIE, especially rectosigmoid disease

• Surgical therapy consists of:
  - Shaving
  - Discoid resection
  - Segmental low anterior or sigmoid resection
Surgical Management

  - Review of 34 articles describing 1889 bowel resections
  - 71 - 93.6% of women were pain free at 1 year
  - 13.9% recurrence of endometriosis at 2-5yr f/u
  - 23.8% clinical pain recurrence at 2-5 yrs
  - 6.4% major bowel complications: 1.9% leakage, 1.8% fistula, 2.7% obstruction, 2.5% hemorrhage, 1% infection
  - Fertility rates 10-33%
Surgical Management

  - Gynecologists in Brazil doing all types of resections
  - Shaving in 22 (10%), discoid resection in 52 (24%), segmental resection in 92 (42%), ileal/cecal resections in 3, appy in 47 (22%)
  - Complete resolution of:
    - Rectal bleeding and painful defecation in 100%,
    - Non-cyclic pain in 90%
    - Dyspareunia in 75%
    - Dysmenorrhea in 59%
  - Complications: 7.6% overall
    - 3 fistulas, 3 obstructions, 2 infections, 1 anastomotic leak, protracted bowel dysfunction in 4
Case 1

- S.A. 41yo P3 s/p R oophorectomy for endometrioma in 2005, TAH 2007,
  - Cyclical rectal bleeding
  - Cyclical sharp, stabbing mid pelvic pain
  - Stabbing pain in rectum with BM, and in LLQ when stool moving through sigmoid
  - Constipation when pain severe
- Consults with GI, colorectal surgery - told she had IBS
Case 1

- **Findings at surgery:**
  - Nodular endo 6-8cm of rectosigmoid on antimesenteric surface
  - Dense adhesions of left ureter to sigmoid, and of left tube and ovary to pelvic sidewall
  - Adhesions of the colon to the vaginal cuff and left sidewall

- **Pathology report:**
  - Submucosal nodule 2.5 x 2 x 1.5cm
Case 2

- **L.B. 51yo P1**
  - Underwent ExLap in 2007 for obstruction
    - R partial colectomy/ileal resection
    - Left oophorectomy
    - Told she had an obliterated CDS and adhesions of right ovary to uterus
  - **Symptoms:**
    - Severe fecal urgency
    - Pencil thin stools
    - Pain upper rectum on left
    - Frequent diarrhea
    - RLQ squeezing/pressure type pain
    - Nausea typically in AMs
Case 2

Long 2.5 x 1.06cm  Trans 2.03 x 1.23 cm
Case 2

- Findings at surgery:
  - Extensive adhesions of small bowel to anterior and lateral abdominal walls
  - Large 4-4.5cm endometrioma of rectosigmoid causing a sharp kink in the lumen
  - Lumen barely admitted 1 finger

- Pathology:
  - 3.5 x 2.5 cm area of mucosal erosion
  - Bowel wall thickening up to 1.5 cm
Case 3

• L.B. 33yo P0
  - Diffuse pelvic pain mostly resolved after bilateral ovarian cystectomies for 7cm endometrioma on left, 4cm on right
  - Found to have 2-3cm nodules on rectosigmoid at time of ovarian cystectomies.
  - Persistent pain with defecation which is present all month long but worse around menses
  - Deep central pelvic constant pain and dyspareunia
  - Cyclical rectal bleeding
Case 3

Tuesday, October 7, 14
Case 3

• Findings at surgery:
  - 2 nodules on the rectosigmoid, 1 at the reflection and 1 about 3 cm higher causing an acute kink of the lumen
  - Adherence of the posterior uterine surface to the bowel wall thus obliterating the culdesac
  - Filmy adhesions of the sigmoid over the left ovary
  - Normal fimbriae; uterus, tubes and ovaries left in situ

• Pathology:
  - Full thickness endometriosis involving 2 small mucosal nodules
  - Bowel wall up to 1 cm in thickness
Case 3
Histology
Summary

- Consider intestinal endo in women with:
  - Pain predominant IBS symptoms AND...
    - History of cyclic pelvic pain
    - Personal or family history of endometriosis
    - Nodularity or point tenderness near culdesac

- Make diagnosis by:
  - Careful history and physical exam
  - Possibly ultrasound or MRI
  - Probably not by colonoscopy
  - Consider referral to endometriosis specialist