Surgery for Endometriosis: Are we helping or Hurting?

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Disclosure:
I have no financial associations to disclose.

CLC

- Endometriosis disparities:

- Endometriosis is most common among Asian women, followed by Caucasian, and is reported less frequently among African-American women
  - Jacoby et al. AOG 2010 Racial and ethnic disparities in benign gynecologic conditions and associated surgeries.
Surgery for Endometriosis: Are we helping or Hurting?

Objectives:

1. The effects and consequences on reproductive health will be reviewed.
2. Medical therapy as an adjuvant to surgical therapy will be discussed.
3. Causes for surgical failure will be reviewed.

ARS 1

• If you are performing surgery for an endometrioma in a woman in her 30s or 40s who desires fertility preservation, do you routinely order a serum AMH?

• 1 - Yes
• 2 - No

ARS 2

• There is level 1 evidence to show that the post operative use of OCPs can reduce the recurrence risk of endometrioma?

• 1 – Yes
• 2 - No
ARS 3

- The recurrence risk of ovarian endometriomas is lower with cystectomy compared with ablation.

- 1 – True
- 2 - False

Is Surgery Helping or Hurting?

<table>
<thead>
<tr>
<th>Helping?</th>
<th>Hurting?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain relief</td>
<td>Multiple surgeries</td>
</tr>
<tr>
<td>Fertility</td>
<td>Ovarian damage</td>
</tr>
<tr>
<td></td>
<td>Delaying the correct diagnosis</td>
</tr>
<tr>
<td></td>
<td>Surgical complications</td>
</tr>
<tr>
<td></td>
<td>Incomplete treatment</td>
</tr>
</tbody>
</table>

What are we learning?

- Incomplete resection of DIE may reduce symptomatic outcomes (Verasrini et al., 2006).
- Radical interventions increase the risk of major complications such as ureteric and rectal injuries (Konink et al., 1996).
- In the absence of histological sampling, the false-positive rate with laparoscopic visualization alone may approach 50% (Wyeks, Br J Obstet Gynaecol 2004).
- Endometriosis is often asymptomatic.
  - 6% - 42% of asymptomatic women undergoing laparoscopic tubal sterilization have endometriosis.
- There is growing that surgical treatment of endometriomas contributes to reduced ovarian reserve (Somigliana et al., 2012; Raffi et al., 2012).
Helping vs. Hurting

- Am I treating an endometrioma at the expense of the ovary?
- Should I be treating with hormonal therapy post operatively?
- Is the endometriosis I am treating, the actual cause of the pain?

Endometriosis: Brief Overview

- Endometriosis is an inflammatory condition characterized by lesions of endometrial-like tissue outside of the uterus and is associated with pelvic pain and infertility.

(Giudice LC. N Engl J Med 2010;362:2389-2398.)

Overview

Endometriosis Symptoms

- dysmenorrhea
- dyspareunia
- heavy menstrual bleeding
- pain at ovulation
- dyschezia
- dysuria
- chronic fatigue

-Kennedy, Hum Reprod, 2005
-Nnoaham, Fertil Steril, 2011
Overview
Endometriosis Likely Affects Immunologically and Genetically Susceptible Individuals through:

- Retrograde endometrial tissue loss during menstruation
- Coelomic metaplasia
- Lymphatic spread
- The underlying cause is uncertain
  - multifactorial including genetic factors with possible epigenetic influences, perhaps promoted through environmental exposures.

Overview
Characteristics


- Endometriosis has elements of a pain syndrome with central neurological sensitization (Stratton. Hum Reprod Update 2011)

Overview
Pain Issues

- Deep infiltrating lesions are often innervated.

- Endometriotic lesions, followed by denervation and re-innervation, may result in accompanying changes in the central nervous system (central sensitization), creating a chronic pain syndrome (Stratton, Human Repro Update 2011).
This illustrates how endometrial lesions can engage the nervous system to give rise to different types of pain associated with endometriosis and co-morbid conditions.


Infertility Associations

- Infertility - strong association between severity of disease and impact on fertility
  - Impaired tubo-ovarian function
  - Ovarian endometrioma
  - Subclinical pelvic inflammation

- Possible reduced oocyte quality, ovarian reserve, and reduced endometrial receptivity to implantation (Lessey Fertil Steril 2011, Raffi JCEM 2012)

- Endometriosis and adenomyosis reduce the chance of success of assisted reproductive treatment (Barnhart, Fertil Steril 2002)

Infertility

<table>
<thead>
<tr>
<th>Help</th>
<th>Harm</th>
</tr>
</thead>
</table>
Endometriomas and Surgery

- Medical therapy is relatively ineffective in the treatment of endometriomas (Renaglia, Human Reprod 2009)
- Endometriomas are found in up to 20% of patients with endometriosis (Redwine, Fertil Steril 1999)
- Two main surgical options: cystectomy vs. cyst ablation
- Cancer Risk?

Endometriosis and Cancer

- Association with clear cell and low-grade serous and endometrioid ovarian cancer (Pearce et al., 2012)
- Overall risk of ovarian cancer remains low
  - Relative risk ranging from 1.3 to 1.9 (Sayasneh et al., 2011)
  - Life-time risk of ovarian cancer is increased from ~1 in 100 to 2 in 100.

Endometriomas Cystectomy vs. Coagulation

- Cystectomy for endometriomas is preferred to drainage and coagulation.
  - Minimize symptom / endometrioma recurrence (Hart et al., 2008).
- Cystectomy performed by highly experienced surgeons has been shown to reduce ovarian volume (Biacchiardi et al., 2011).
Cystectomy

Help

• Less recurrence

Harm

• Ovarian reserve
• Ovarian volume

Cystectomy: Recurrence
Hart, Cochrane Database Review 2008

Cystectomy: Ovarian Reserve
Raffi, JCEM 2012: Meta-analysis.
Weighted mean differences in serum AMH after surgery for endometrioma
Cystectomy: Ovarian Reserve

Raffi, JCEM 2012: Meta-analysis.
Weighted mean differences in serum AMH after surgery for endometrioma: Pooled results for studies with analysis of changes in AMH stratified by baseline 3.1 ng/ml

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Mean Preop</th>
<th>SD Preop</th>
<th>Mean Postop</th>
<th>SD Postop</th>
<th>% Change</th>
<th>95% CI</th>
<th>Mean Difference</th>
<th>95% CI</th>
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<td>3.1</td>
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<td>Hossain 2011</td>
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<td>0.3</td>
<td>0.0</td>
<td>0.0</td>
<td>3.0(2.9, 3.1)</td>
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<tr>
<td>Kaller 2011</td>
<td>3.2</td>
<td>0.3</td>
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<td>0.0</td>
<td>3.2(3.0, 3.3)</td>
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<tr>
<td>Lee 2011</td>
<td>3.1</td>
<td>0.3</td>
<td>3.2</td>
<td>0.3</td>
<td>3.3</td>
<td>0.0</td>
<td>3.2(3.1, 3.3)</td>
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<tr>
<td>Testek et al 2009</td>
<td>3.1</td>
<td>0.3</td>
<td>3.2</td>
<td>0.3</td>
<td>3.3</td>
<td>0.0</td>
<td>3.2(3.1, 3.3)</td>
<td></td>
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<tr>
<td>Total (N=5)</td>
<td>3.1</td>
<td>0.3</td>
<td>3.2</td>
<td>0.3</td>
<td>3.3</td>
<td>0.0</td>
<td>3.2(3.1, 3.3)</td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 3.1 (P = 0.0016)

AMH levels according to the presence of an OMA and to past OMA surgery.
Streuli, Hum Reprod 2012

AMH levels according to the type of endometriosis and prior OMA surgery.
Streuli, Hum Reprod 2012
Other Infertility Issues

- Laparoscopic surgical removal of endometriosis is effective in improving fertility in stage I and II endometriosis (Jacobson et al., 2010).
- No RCTs have to date assessed whether surgery improves fertility in stage III and IV endometriosis and in deep endometriosis.
- The functional appearance of the fallopian tubes and ovaries at the end of the laparoscopic procedure appears to contribute to the chance of natural conception post-operatively (Adamson and Pasta, 2010).

Expert Recommendations*

- Laparoscopic cystectomy for endometriomas >4 cm in diameter improves fertility more than drainage (Jart et al., 2008).
- Avoid removing normal ovarian tissue and thus impacting on ovarian reserve.
- Suturing for hemostasis might maintain ovarian reserve more effectively than electrosurgical hemostasis (Pellicano et al., 2008).
- Minimization of the use of energy modalities in hemostasis.
- Young women, for whom fertility is a consideration, might benefit from discussion of the option of oocyte freezing prior to undergoing ovarian endometrioma surgery, especially if bilateral.


Post Op Considerations: Should we treat with hormones?

- Evidence does not support the use of short-term pre- or post-operative medical treatment for improving pain outcomes or recurrence rates (Cochrane Review 2011).
- Post op OCP use reduces endometrioma recurrence rate after cystectomy (Seracchioli et al., 2010)
  - Larger RCT (n=239) not included in Cochrane review
  - 8% recurrence in continuous OCP users (24 months)
  - 29% recurrence rate in non users (24 months)
Levonorgrestrel IUD after surgery
Cochrane Review 2013

- 3 RCTs
- Limited but consistent evidence the LNG-IUD use reduces dysmenorrhea.
- Recurrence data are not well studied.
Post operative LNG-IUD Cochrane Review 2013

Pelvic Pain and Endometriosis Cochrane Review 2009

What about the patients who don’t get better?
Possibilities to Consider

• **Wrong diagnosis (no histology)**
  - The false-positive rate with laparoscopic visualization alone may approach 50% especially in women with minimal or mild endometriosis (Wykes, Br J Obstet Gynaecol 2004).

• **True, true, unrelated**
  - A biopsy proven endometriosis exists
  - Patient has pain (centralized, neuropathic, or other peripheral)
  - Endometriosis happens to be present in an incidental form.

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Asymptomatic Endometriosis

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![Graph showing Asymptomatic Endometriosis with conditions and treatments.](image)
Case

• 32 y/o G2 P2 with 10 years history of CPP
• Diagnosed with endometriosis, adhesions.
• 8 pelvic surgeries
  • L-scope 99, 01, RSO 02, LAVH 03, L-scope 04, 05
  • LSO 06, L-scope 08 (peritoneal stripping)
• Pain is constant, daily.
• OCP, GnRH agonists, NSAIDS don’t help
• Daily oxycodone, heating pad gives provide some relief.

Case Continued

• She experienced relief for 3 to 6 months after each surgery.
• She heard you were a great surgeon and is sure that the 9th surgery will make a positive difference.
• She expresses that she feels that endometriosis has ruined her life.

Case Continued

• Does her case sound like endometriosis?
  – Constant, daily pain, refractory to all therapy.
• Endometriosis-related pain is understudied.
  – Only 3 studies in the Cochrane database for endometriosis-related pain.
  – 6% - 42% of asymptomatic women undergoing laparoscopic tubal sterilization have endometriosis.
• Endometriosis is often asymptomatic.
Pain Syndromes
Characterized by widespread Hyperalgesia / Allodynia

Tension/migraine headache
Non cardiac Chest Pain
Irritable bowel syndrome
Nondermatomal paresthesias
TMJD syndrome
Idiopathic LBP
Failed back surgery syndrome
Failed pelvic surgery syndrome
Fibromyalgia, CWP
Neuromuscular pain syndromes

Mechanistic Characterization of Pain
Combinations may be present

<table>
<thead>
<tr>
<th>Periphera</th>
<th>Neuropathic</th>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>Nerve damage/entrapment</td>
<td>Diffuse hyperalgesia</td>
</tr>
<tr>
<td>NSAID / Opioids</td>
<td>NSAID, opioids, TCAa, SNRIs, NSRIs, anticonvulsants</td>
<td>Responsive to neuroactive compounds altering levels of neurotransmitters in pain transmission</td>
</tr>
<tr>
<td>Procedures effective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Diabetic neuropathy</td>
<td>FM, IBS, IC</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Post herpetic neuralgia</td>
<td></td>
</tr>
<tr>
<td>Cancer pain</td>
<td>Trigeminal neuralgia</td>
<td></td>
</tr>
<tr>
<td>Early endometriosis</td>
<td>Pudendal neuralgia</td>
<td></td>
</tr>
</tbody>
</table>

Differential Diagnosis

<table>
<thead>
<tr>
<th>Gynecologic Causes</th>
<th>Non Gynecologic Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometritis / adenomyosis</td>
<td>Myofascial pain syndrome</td>
</tr>
<tr>
<td>Primary dysmenorrhea</td>
<td>IBS (Irritable)</td>
</tr>
<tr>
<td>Adhesions</td>
<td>IBS (Inflammatory)</td>
</tr>
<tr>
<td>PID / tubal dz</td>
<td>Carcinoma of the colon</td>
</tr>
<tr>
<td>Pelvic Varicosities</td>
<td>Diverticular disease</td>
</tr>
<tr>
<td>Pain of uterine origin</td>
<td>Chronic Appendicitis</td>
</tr>
<tr>
<td>Levator ani syndrome</td>
<td>Constipation</td>
</tr>
<tr>
<td>Vulvar vestibulitis</td>
<td>Renal / ureteral stone</td>
</tr>
<tr>
<td>Retained ovary syndrome</td>
<td>L.C. / PBS</td>
</tr>
<tr>
<td>Ovarian remnant syndrome</td>
<td>Cystitis</td>
</tr>
<tr>
<td>Neuropathic pain syndrome</td>
<td>Urethral syndrome</td>
</tr>
<tr>
<td>Chronic ovarian torsion?</td>
<td>Urethral diverticulum</td>
</tr>
<tr>
<td>Gynecologic malignancy</td>
<td>Hernia</td>
</tr>
<tr>
<td>Fibroids</td>
<td>S.I. joint malrotation</td>
</tr>
<tr>
<td>Ovulatory pain</td>
<td>Somatization disorder</td>
</tr>
<tr>
<td>Pudendal neuralgia</td>
<td>Adhesions</td>
</tr>
<tr>
<td></td>
<td>Compression of lumbar vertebrae</td>
</tr>
<tr>
<td></td>
<td>Piriformis syndrome</td>
</tr>
</tbody>
</table>
Neural Influences on Pain and Sensory Processing

Facilitation
- Substance P
- Glutamate
- Serotonin
- Nerve Growth Factor
- Cholecystokinin

Inhibition
- DNIP
- Norepinephrine
- Dopamine
- GABA
- Cannabinoids
- Adenosine

Adapted from D Clauw MD

Viscero-Somatic Convergence or Convergence-Projection

Is This Central Pain?

- Overload of nociceptive stimuli to DH resulting in metabolic, biochemical, and electrophysiologic changes.
- Activation of NMDA receptors within DH
- Loss of inhibition at DH / ↓ nociceptive threshold (alldynia)
- Duration + severity may result in permanent biochemical changes = centralization
- Exaggerated reflex output with end organ dysfunction / spontaneous firing of DH neurons
### Non-Opioid Adjuvants: Ion Blockers

<table>
<thead>
<tr>
<th>Active Drug</th>
<th>+ trials/total</th>
<th>mean daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>4/4</td>
<td>1800 mg</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>&gt;10</td>
<td>600 mg</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>3/4</td>
<td>567 mg</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>1/2</td>
<td>300 mg</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1/1</td>
<td>400 mg</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>2/5</td>
<td>340 mg</td>
</tr>
</tbody>
</table>

### Antidepressants and Neuropathic Pain RCTs

<table>
<thead>
<tr>
<th>Active Drug</th>
<th>+ trials/total</th>
<th>mean daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>5/5</td>
<td>80 mg</td>
</tr>
<tr>
<td>Imipramine</td>
<td>3/3</td>
<td>150 mg</td>
</tr>
<tr>
<td>Desipramine</td>
<td>2/2</td>
<td>184 mg</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1/1</td>
<td>40 mg</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>0/1</td>
<td>--</td>
</tr>
<tr>
<td>Citalopram</td>
<td>1/2</td>
<td>25 mg</td>
</tr>
</tbody>
</table>

### Reuptake Inhibitors

<table>
<thead>
<tr>
<th>SSRI</th>
<th>SNRI</th>
<th>NSRI</th>
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</thead>
<tbody>
<tr>
<td><em>fluoxetine</em></td>
<td><em>venlafaxine</em></td>
<td><em>milnacipran</em></td>
</tr>
<tr>
<td>sertraline</td>
<td>duloxetine</td>
<td></td>
</tr>
<tr>
<td>paroxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>escitalopram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>citalopram</td>
<td></td>
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</table>

*fluoxetine becomes a dual reuptake inhibitor at >45 mg*
NNT

(No of patients that need to be treated to achieve therapeutic response)

<table>
<thead>
<tr>
<th>Category</th>
<th>NNT (NPP)</th>
<th>NNT (CP)</th>
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</thead>
<tbody>
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<td>TCA(^1)</td>
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<td></td>
</tr>
<tr>
<td>SSRI(^1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pregabalin(^2)</td>
<td>3.9 - 5.0</td>
<td>5.6 - 11</td>
</tr>
<tr>
<td>Gabapentin(^3)</td>
<td>4.3</td>
<td></td>
</tr>
</tbody>
</table>


Summary

• Consider ovarian reserve prior to laparoscopic surgery in the woman experiencing infertility (Pellicano et al., 2008)

• There is growing that surgical treatment of endometriomas contributes to reduced ovarian reserve (Somigliana et al., 2012; Raffi et al., 2012).

Summary

• Evidence is still lacking to guide the best surgical approach to deep endometriosis.

• Bowel surgery should proceed on the basis of shared decision-making after thorough consideration of risks versus benefits.

• There is evidence to suggest the use of post-operative OCPs may lower the recurrence rate of endometriomas.
Summary

• Distinguish between cyclic, acute, and chronic causes of pain.

• Treat peripheral pain with peripherally targeted therapies.

• Treat central pain with centrally targeted therapies.