Thoughtful Management of Endometriosis

DATE: February 2017 PRESENTED BY: Amanda Sadecky MD
Disclosures

- I am passionate about treating women with pelvic pain
- I have no relevant financial disclosures
What is endometriosis?
Endometriosis

“The definitive diagnosis of endometriosis only can be made by histology of lesions removed at surgery”
Pathogenesis of Endometriosis

- Ectopic endometrial glands & stroma

- Altered hormonal response
  - COX-2 activity
  - Prostaglandins
  - aromatase activity
  - Estrogen

- Progesterone resistance allows for amplified local estrogenic effect
Why Medical Therapy?

• “Endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures.”
  – Practice Committee of the American Society for Reproductive Medicine
Goals

- Reduce Pain
- Treat symptomatic pelvic masses
  While...
- Minimizing side effects
- Reducing surgical complications
- Considering cost
- Preserving desired fertility
- Avoid premature menopause
Treatment

- NSAIDs
- Hormonal
  - Combined oral contraceptives
  - Gonadotropin-releasing hormone (GnRH) agonists
  - Progestins
  - Androgens (Danazol)
  - Aromatase inhibitors
  - Selective Estrogen Receptor Modulators (SERMS)
- Anti-TNF (Tumor Necrosis Factor)
NSAIDs

- Only one study of NSAIDs met Cochrane criteria
- 24 women with endometriosis classified as mild, moderate or severe each received each treatment group for two cycles, 6 lost to follow up
  - Naproxen sodium 275mg QID
  - Placebo QID
- Pain relief for Naproxen vs Placebo: OR 3.27 CI (0.61-17.69)

Cochrane Allen 2009
Kauppila 1985
COX-2 Inhibitor (VIOXX)

- One RCT of Rofecoxib (COX)-2 inhibitor
- 28 women with surgically diagnosed stage I/II endometriosis
  - Rofecoxib: 25mg po q day (n=16)
  - Placebo: (n=12)
- 6 months of treatment with Visual Analog Scale evaluation of pain
- Improvement of pain & dyspareunia in treatment arm

Cobellis 2004
NSAIDs

• Benefits:
  – Low cost, few side effects

• Disadvantages:
  – No high quality data showing great benefit

• NSAIDs well documented to be beneficial in treatment of dysmenorrhea

Marjoribanks 2015
Oral Contraceptives

- First line treatment for endometriosis
- Relative paucity of data, especially for low dose OCP formulations
- ? Mechanism of action
  - Atrophy of ectopic endometrial tissue
- Advantages
  - Can be taken long term, low cost, contraception, menstrual regulation, safe
- Disadvantages
  - Blood clots, daily dosing
Oral Contraceptives

• 100 patients randomized
  – OCP (n=51, 86% completed study)
  – Placebo (n=49, 88% completed study)
• Dysmenorrhea was primary outcome, measured by Visual Analog Scale
  – OCP arm decreased by 2.0
  – Placebo arm decreased by 0.6
• Change in size of endometriomas and non-menstrual pain score both significantly decreased in treatment arm

Harada 2008
Change in mean dysmenorrhea score $P<0.001$

Harada 2008
Continuous OCPs

- 50 women with surgery proven endometriosis who had recurrent dysmenorrhea despite cyclic OC use
- Two year trial
- 9 patients stopped treatment for various reasons
- 80% reported being satisfied or very satisfied

Vercellini 2003
Rings & Patch

• 207 women with surgically proven endometriosis
• Pt self selected either ring or patch to be used in a continuous fashion
Rings & Patch

<table>
<thead>
<tr>
<th></th>
<th>Ring</th>
<th>Patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts enrolled</td>
<td>123</td>
<td>84</td>
</tr>
<tr>
<td>Withdrew</td>
<td>44 (36%)</td>
<td>51 (61%)</td>
</tr>
<tr>
<td>Leaving</td>
<td>79</td>
<td>33</td>
</tr>
<tr>
<td>Cyclic use</td>
<td>36 (46%)</td>
<td>14 (42%)</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>88 (72%)</td>
<td>40 (48%)</td>
</tr>
</tbody>
</table>

(intention to treat)
Rings & Patch

Vercellini 2007
GnRH agonists

- Generally initiated in patients who have not responded to OCPs or NSAIDs
- Use stimulates pituitary release of LH and FSH
- Chronic use then causes down regulation
- Suppresses ovarian follicular growth and ovulation
- Decreases circulating estradiol and progesterone
- Induces postmenopausal state
- Inhibits endometrium cell growth
# Approved for Endometriosis

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupron</td>
<td>Leuprolide Acetate</td>
<td>3.75mg IM Monthly 11.25mg IM every three months</td>
</tr>
<tr>
<td>Zoladex</td>
<td>Goserelin</td>
<td>3.6mg SQ Monthly</td>
</tr>
<tr>
<td>Synarel</td>
<td>Nafarelin acetate</td>
<td>200mg nasally BID, alternate nostrils</td>
</tr>
</tbody>
</table>

Clinical Gynecology 2015
Efficacy

• Randomized, double blinded study of 95 patients suspected to have endometriosis
  – Lupron (n=49) 38 (78%) surgically proven
  – Placebo (n=46) 40 (87%) surgically proven

• Treatment for three months

• Evaluated for dysmenorrhea, pelvic pain and pelvic tenderness
Table 1. Mean Physician-Evaluated Pain Scores at Baseline and Week 12

<table>
<thead>
<tr>
<th></th>
<th>n (wk 12)</th>
<th>Score at baseline</th>
<th>Score at wk 12</th>
<th>Depot leuprolide vs placebo mean difference at wk 12*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysmenorrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depot leuprolide</td>
<td>44</td>
<td>3.1</td>
<td>1.0</td>
<td>-1.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>44</td>
<td>3.2</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Pelvic pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depot leuprolide</td>
<td>44</td>
<td>3.2</td>
<td>1.9</td>
<td>-1.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>44</td>
<td>3.1</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Pelvic tenderness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depot leuprolide</td>
<td>44</td>
<td>2.7</td>
<td>1.5</td>
<td>-0.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>44</td>
<td>2.6</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Deep dyspareunia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depot leuprolide</td>
<td>30</td>
<td>2.9</td>
<td>1.6</td>
<td>-1.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>33</td>
<td>2.8</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Pelvic induration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depot leuprolide</td>
<td>44</td>
<td>2.0</td>
<td>1.4</td>
<td>-0.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>44</td>
<td>2.2</td>
<td>2.1</td>
<td></td>
</tr>
</tbody>
</table>

Pain scores: 1 = none, 2 = mild, 3 = moderate, 4 = severe.

*P ≤ .001.
Side Effects

- Hot flashes
- Amenorrhea
- Vaginal dryness
- Osteopenia (reversible with short term use)
Add Back Therapy

- Randomized, double blinded 1 year trial of 201 patients with pain in setting of endo
- All received IM Lupron 3.75mg q 4 weeks
  - A: Placebo Estrogen and progesterone
  - B: Norethindrone acetate 5mg, placebo estrogen
  - C: Norethindrone acetate 5mg, CEE 0.625mg
  - D: Norethindrone acetate 5mg, CEE 1.25mg
- All groups received 1g of calcium daily

Hornstein 1998
Add Back Therapy

• Pelvic pain assessed monthly
  – No difference between groups
• Bone density at 24 and 52 weeks
  – 6.3% drop in bone density in placebo group
  – No change in other groups
• Higher drop out rate for pelvic pain symptoms in high dose estrogen group
• Pilot study of 5 patients taking Lupron for 10 years showed stable bone mineral density

Hornstein 1998
Progestins

- Cause atrophy of endometriosis
- Inhibit pituitary gonadotropin secretion
- Down regulate ovarian hormone production
- May be effective in reducing implants and recurrent disease
- Do not cause bone loss
- Inexpensive
- Cause weight gain, irregular bleeding, mood changes
Oral Progestins

• Medroxyprogesterone acetate
  – (10mg TID, max 100mg q day)

• Norethindrone acetate
  – (5mg q day, max 15mg q day)

• Dinogest
  – (2mg po q day)

Brown Cochrane review 2012
Aygestin (norethindrone acetate)

- FDA approved for treatment of endometriosis pain
- Start at 5mg po daily x 2 weeks
- Increase by 2.5mg every two weeks until 15mg reached or symptoms improve
- Continue for six to nine months or until “annoying breakthrough bleeding demands temporary termination”

Dinogest

• Synthetic oral progestin
• 2mg orally daily
• Minimally affects bone density, higher incidence of abnormal bleeding

Strowitzki 2010
Dinogest

- 252 patients with endo, treated for 24 weeks with
  - Dinogest (n=124) 88% completed trial
  - Lupron (n=128) 94% completed trial
- Measured reduction in VAS, bleeding episodes, BMD, hot flashes

Strowitzki 2010
Dinogest

![Graph showing VAS scores over study duration with p<0.0001 for non-inferiority.](image)
Injectable

• Depot medroxyprogesterone (DMPA)
  – 150mg IM q 3 months
• FDA approved for treatment of endometriosis pain
• Side effects: Irregular bleeding, nausea, breast tenderness, depression, loss of BMD (reverts back to baseline with in 12 months), delay in pregnancy
Injectable

- 300 patients with laparoscopically diagnosed endometriosis
  - DMPA
  - Lupron
- Evaluated dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, induration, BMD, productivity
Injectable

Crosinani 2006
Implant

- 41 patients with endometriosis
  - Implanon (n=21)
  - DMPA (n=20)
- Treated for a year, evaluated pain on VAS, side effects, vaginal bleeding, overall satisfaction
  - Implanon pain decreased 68%
  - DMPA pain decreased 53%
- Other outcomes similar
LNG-IUD

- Not FDA approved for treatment of endometriosis pain
- Two studies showed reduction in pain with LNG-IUD
- One study showed same efficacy of reducing pain as GnRH agonists
LNG-IUD

- Three year study of use of LNG-IUD in 34 women with laparoscopically confirmed endo
- At 36 months 19 (56%) were still using IUD, similar to continuation rate for IUDs placed for contraception
- Drop in VAS Pain score from 7.7 to 2.7

Lockhat 2005
LNG-IUD

• Double blind* randomized controlled trial in women with laparoscopically confirmed endo
  – LNG-IUD (n=28)
  – Control (n=27)

• Followed for 12 months, primary outcome of pain Visual Analog Scale
**LNG-IUD**

<table>
<thead>
<tr>
<th></th>
<th>IUD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pts enrolled</strong></td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td><strong>At 12 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Change in VAS Scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>-8.1</td>
<td>-5.0</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>-4.9</td>
<td>-2.2</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>7.4%</td>
<td>39.1% (p=.014)</td>
</tr>
<tr>
<td><strong>Number needed to treat</strong></td>
<td>= 3</td>
<td></td>
</tr>
</tbody>
</table>

Tanmahasamut 2012
Danazol (Danocrine)

- First drug approved by FDA (1970s) for treatment of endometriosis
- 100-400mg po BID/TID
- Effective for treatment of endometriosis but limited by masculinizing side-effects
- Suppresses gonadotropins, weak androgen
- Causes atrophy of endometrium
- Prevents ovulation by suppressing LH surge
- Side effects: hirsuitism, acne, hot flashes, weight gain, fetal effects

Farquhar 2007
Danazol (Danocrine)

- Laparoscopic confirmation of endometriosis
- Three arms treated for six months
  - Danazol (n=18) 200mg po TID
  - Medroxyprogesterone acetate (n=16) 100mg daily
  - Placebo (n=17)
- Clinical exams at 1, 3, 6 & 12 months
- Second look laparoscopy at 12 months

Farquhar 2007  Telimaas 1987
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Danazol N</th>
<th>Danazol Mean(SD)</th>
<th>Placebo N</th>
<th>Placebo Mean(SD)</th>
<th>Mean Difference IV,Fixed,95% CI</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three months of treatment</td>
<td>18</td>
<td>2.25 (2.54)</td>
<td>17</td>
<td>7.2 (2.47)</td>
<td>[4.95, -6.61, -3.29]</td>
<td>100.0</td>
</tr>
<tr>
<td>Telmaa 1987a</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>18</td>
<td></td>
<td>17</td>
<td></td>
<td>[4.95, -6.61, -3.29]</td>
<td>100.0</td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 5.84 (P &lt; 0.00001)</td>
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<tr>
<td>Six months of treatment</td>
<td>18</td>
<td>1 (2.97)</td>
<td>17</td>
<td>6.7 (2.47)</td>
<td>[5.70, -7.51, -3.89]</td>
<td>100.0</td>
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<tr>
<td>Telmaa 1987a</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>18</td>
<td></td>
<td>17</td>
<td></td>
<td>[5.70, -7.51, -3.89]</td>
<td>100.0</td>
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<tr>
<td>Heterogeneity: not applicable</td>
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<tr>
<td>Test for overall effect: Z = 6.19 (P &lt; 0.00001)</td>
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<td></td>
</tr>
<tr>
<td>Six months after stopping treatment</td>
<td>18</td>
<td>3 (2.54)</td>
<td>17</td>
<td>10.5 (3.09)</td>
<td>[7.50, -9.38, -5.62]</td>
<td>100.0</td>
</tr>
<tr>
<td>Telmaa 1987a</td>
<td></td>
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<td></td>
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</tr>
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<td>Subtotal (95% CI)</td>
<td>18</td>
<td></td>
<td>17</td>
<td></td>
<td>[7.50, -9.38, -5.62]</td>
<td>100.0</td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 7.82 (P &lt; 0.00001)</td>
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</tr>
<tr>
<td>Test for subgroup differences: Chi² = 4.08, df = 2 (P = 0.13), I² = 51%</td>
<td></td>
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</tr>
</tbody>
</table>
Surgical Management

- Severe, incapacitating or acute symptoms
- Symptoms that have failed to resolve or have worsened under medical management
- Adnexal mass suspicious for malignancy
- Patient preference
Surgical Pain Outcomes

• Abbott, et al, 2004
  – Randomized, blinded, crossover study to examine effect of l/s surgery on pain and QOL for women with all stages of endometriosis
  – 52 women were randomized to delayed or immediate surgery with 39 completing study
  – Completed VAS and 3 QOL instruments preop, 6 months (prior to 2nd surgery) and 12 months

Abbott, et al, 2004
# Surgical Pain Outcomes

## Change in overall level of pain reported after surgery.

<table>
<thead>
<tr>
<th></th>
<th>DSG</th>
<th>ISG</th>
<th>DSG vs. ISG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any improvement in pain, n (%)</td>
<td>6 (32)</td>
<td>16 (80)</td>
<td>$\chi^2 = 9.3, P = .002$</td>
</tr>
<tr>
<td>No change/worse pain, n (%)</td>
<td>12 (62)</td>
<td>4 (20)</td>
<td>$Z = -2.5, P = .012$</td>
</tr>
<tr>
<td>VAS* change in pain, score (range)</td>
<td>0 (0–100)</td>
<td>30 (0–95)</td>
<td></td>
</tr>
<tr>
<td>Surgery 2*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any improvement in pain, n (%)</td>
<td>15 (83)</td>
<td>8 (53)</td>
<td>$\chi^2 = 3.88, P = .13$</td>
</tr>
<tr>
<td>No change/worse pain, n (%)</td>
<td>3 (17)</td>
<td>7 (47)</td>
<td>$Z = -1.22, P = .26$</td>
</tr>
<tr>
<td>VAS change in pain, score (range)</td>
<td>82.5 (0–100)</td>
<td>50 (0–100)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Patients were asked to report on their pain relief 6 mo after surgery. For surgery 1, this was immediately before surgery 2 and for surgery 2 this was 12 mo from surgery 1.

* Visual analogue scale, where 0 = no change in pain and 100 = complete relief of pain.

* Patients were asked to report on the improvement in overall level of pain after surgery 2, not compared with baseline.

**Surgical Pain Outcomes**

<table>
<thead>
<tr>
<th>Quality of life outcomes</th>
<th>DSG</th>
<th>DSG vs. normal</th>
<th>ISG</th>
<th>ISG vs. normal</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean difference (CI), P</td>
<td>Mean (SD)</td>
<td>Mean difference (CI), P</td>
<td>DSG vs. ISG</td>
</tr>
<tr>
<td>EQ-5D index summary, mean normal score = 0.91 (SD = 0.15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.68 (0.28)</td>
<td>-0.22 (-0.35, -0.08), P=.003</td>
<td>0.68 (0.28)</td>
<td>-0.21 (-0.35, -0.07), P=.004</td>
<td>P=.88</td>
</tr>
<tr>
<td>6 mo</td>
<td>0.74 (0.23)</td>
<td>-0.16 (-0.28, -0.04), P=.01</td>
<td>0.77 (0.25)</td>
<td>-0.13 (-0.26, -0.01), P=.03</td>
<td>P=.07</td>
</tr>
<tr>
<td>12 mo</td>
<td>0.82 (035-1)</td>
<td>-0.08 (-0.20, 0.02), P=.10</td>
<td>0.85 (0.73-1)</td>
<td>-0.03 (-0.08, 0.02), P=.34</td>
<td>P=.51</td>
</tr>
<tr>
<td>EQ-5D VAS summary, mean normal score = 85.3 (SD = 14.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>66.1 (19.5)</td>
<td>-19.1 (-28.5, -9.8), P=.0001</td>
<td>77.5 (14.9)</td>
<td>-7.8 (-15.2, -0.4), P=.04</td>
<td>P=.07</td>
</tr>
<tr>
<td>6 mo</td>
<td>65.9 (21.3)</td>
<td>-19.3 (-32.2, -6.4), P=.006</td>
<td>83.6 (10.8)</td>
<td>-4.3 (-8.8, 0.22), P=.54</td>
<td>P=.01</td>
</tr>
<tr>
<td>12 mo</td>
<td>82.7 (16.2)</td>
<td>-2.6 (-10.3, 5.4), P=.51</td>
<td>88.6 (10.4)</td>
<td>3.3 (-1.4, 8.1), P=.15</td>
<td>P=.23</td>
</tr>
<tr>
<td>SF-12 physical component score, mean normal score = 52.8 (SD = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>40.1 (8.1)</td>
<td>-12.3 (-16.5, -8.2), P=.0001</td>
<td>43.5 (8.1)</td>
<td>-9.3 (-13.2, -5.4), P=.0001</td>
<td>P=.27</td>
</tr>
<tr>
<td>6 mo</td>
<td>45.5 (10.0)</td>
<td>-7.2 (-12.4, -1.9), P=.01</td>
<td>48.2 (7.6)</td>
<td>-4.6 (-8.1, -0.9), P=.02</td>
<td>P=.36</td>
</tr>
<tr>
<td>12 mo</td>
<td>52.4 (4.9)</td>
<td>-0.35 (-2.7, 2.0), P=.35</td>
<td>51.2 (6.1)</td>
<td>1.5 (-4.5, 1.4), P=.36</td>
<td>P=.60</td>
</tr>
<tr>
<td>SF-12 mental component score, mean normal score = 51.9 (SD = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>43.5 (12.9)</td>
<td>-8.3 (-14.9, 1.7), P=.01</td>
<td>42.8 (9.1)</td>
<td>-9.1 (-13.5, -5.6), P=.0001</td>
<td>P=.84</td>
</tr>
<tr>
<td>6 mo</td>
<td>45.3 (11.8)</td>
<td>-6.5 (-12.8, -0.18), P=.04</td>
<td>47.6 (9.7)</td>
<td>4.3 (-8.8, 0.22), P=.06</td>
<td>P=.55</td>
</tr>
<tr>
<td>12 mo</td>
<td>49.5 (9.8)</td>
<td>-2.4 (-7.1, 2.3), P=.22</td>
<td>53.1 (8.2)</td>
<td>1.2 (-2.7, 5.1), P=.44</td>
<td>P=.19</td>
</tr>
</tbody>
</table>

*Note: CI = 95% confidence interval.
*a Baseline vs. 6 mo.
*b 6 mo. vs. 12 mo.
*c Baseline, 6-mo, and 12-mo comparison (Friedman test).

Surgical Pain Outcomes

• L/S excision is successful in treating endo-associated pain in short-term
• May also improve some aspects of QOL
• There is a placebo response rate (33%)
Surgical Pain Outcomes

- Jacobson, et al, 2010 (Cochrane Review)
  - To assess effectiveness of l/s surgery in the treatment of pelvic pain associated with endo
  - Included RCTs comparing l/s surgical intervention with medical Rx and/or dx l/s only
  - 5 RCTs were identified
  - Significant advantage of l/s surgery at 6 mo f/u (OR 5.72, CI 3.09-10.6)
  - Significant advantage of l/s surgery at 12 mo f/u (OR 7.72, CI 2.97-20.06)
Take Home

- Medical treatment of endometriosis is best done with a stepwise approach
- Patients may respond better to different therapies
- Important tool in our treatment of endometriosis
- Great deal of research still needed
Proposed Treatment Algorithm

- Trial of NSAIDs or cyclic OCPs
- Trial of continuous OCPs/Nuvaring
- Trial of alternate medical management

Surgery + Medical suppression
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>Type of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Dysmenorrhea</td>
<td>First-line</td>
</tr>
<tr>
<td>Combined oral contraceptives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclic</td>
<td>Dysmenorrhea</td>
<td>First-line</td>
</tr>
<tr>
<td>Continuous</td>
<td>Dysmenorrhea, noncyclic chronic pelvic pain</td>
<td>Second-line</td>
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<tr>
<td>Progestins</td>
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<td></td>
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<tr>
<td>Medroxyprogesterone acetate</td>
<td>Dysmenorrhea, noncyclic chronic pelvic pain</td>
<td>Second-line</td>
</tr>
<tr>
<td>Levonorgestrel intrauterine</td>
<td></td>
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<tr>
<td>system</td>
<td>Dysmenorrhea, dyspareunia</td>
<td>Second- or third-line</td>
</tr>
<tr>
<td>GnRH agonists</td>
<td>Dysmenorrhea, dyspareunia</td>
<td>Second- or third-line</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>Dysmenorrhea, noncyclic chronic pelvic pain</td>
<td>Third-line</td>
</tr>
<tr>
<td>Danazol</td>
<td>Dysmenorrhea, noncyclic chronic pelvic pain</td>
<td>Second- or third-line</td>
</tr>
</tbody>
</table>
Works Cited