Management of Endometriosis: New Tricks for an Old Disease

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Reproductive Endocrinology and Infertility

Endometriosis

- Affects 2.5...3.3...5% of reproductive age women
- Dx’d in 20...38...68% infertile women
  - 19 – 73% with pain
  - 50 – 70% with pain not responsive to medical management
- Women seen 5 times and 9.28 years with symptoms before DX
  (mean 4.2 MD seen)

“Old Disease......New or worsening Problem?”
Presentation

• NONE
• Cyclic Pain (Dysmenorrhea, Dyspareunia, Dyschezia)
• Chronic Pain
• Infertility
• Hemulatory, atochezia, optyosis, epistaxis

Findings

• Pain
• Uterosacral nodularity
• Fixed uterus
• Lateral cervical deviation
• Bluish nodules
• Imaging (Ultrasound > MRI)

Pathogenesis

• Retrograde menstruation
• Immunologic abnormalities
• Endometrial disorders
• Peritoneal dysfunction
• Altered Immune Function
• Altered Steroidogenesis
• Genetic predisposition / Environmental Exposures
Diagnosis

- Surgical
- GLAND and STROMA on PATHOLOGY

Differential Diagnosis

- Infection
- Adhesions
- Mullerian abnormalities
- GI
- GU
- Musculoskeletal

Staging endometriosis

- Operative
- Based on location, diameter, and depth of implants
- Location and amount of adhesions

- Stage I – MINIMAL 1-5
- Stage II – MILD 6-15
- Stage III – MODERATE 16-40
- Stage IV – SEVERE >40
Mechanisms of infertility in pt with endometriosis

- Tubal obstruction
- Pelvic adhesions
- Ovarian endometriomas
- Limited access to fimbriae
- Limited fimbrial mobility
- Macrophage enriched peritoneal fluid
- Defect in endometrial receptivity (decreased integrin expression)

Continued...

- Anovulation
- Endocrine dysfunction (P, E2, LH)
- Corpus luteum insufficiency
- Hyperprolactinemia
- Autoimmunity
- Prostaglandins/thromboxane/leukotrienes
Peritoneal fluid embryotoxicity

- Endometriosis produces an intraperitoneal inflammatory response
- Elevated levels of IL-6 and TNF alpha
- PF in pts with endometriosis shown to be embryotoxic in lab studies
- No correlation between severity of disease and embryotoxicity

Treatments

- Lifestyle Modification?
- Medical
- Surgical
- Expectant

Endometriosis and Diet

256 studies, 11 suitable for analysis
(10 case and 1 cohort)
- Fish, omega-3 polyunsaturated fatty acids
- Trans fat
- Milk, Vitamin D
- Fiber
- Refined carbohydrates
- Soy
- Coffee
Endometriosis: Pain Treatment

• NSAIDS
• Hormone Suppression is hallmark of therapy
  • Oral Contraceptives (consider continuous)
  • Lupron (pseudomenopause) +/- addback
• Progesterone
  • Norethindrone Acetate
  • MPA
  • IUD (levonorgestrel)
• Androgen
  • Vaginal
• Aromatase Inhibitors (letrozole)
  • Possible adjunct to Lupron

Endometriosis: Pain Treatment

• CNS therapy
  • SSRIs
• Surgery – conservative vs. radical
  • Laparoscopic (63-90% relief at 6-12 months)
    • Excision
    • Ablation
    • Cautery
  • Definitive – TAH BSO
    (high rate of recurrence with just TAH)
  • Adjunct hormonal suppression

Medical treatment - Infertility

• No drug is better than any other in the treatment of endometriosis associated infertility.
• No drug results in greater fertility than placebo
• Delays fertility
Rectovaginal Endometriosis

- 12 patients with laparoscopically proven disease
- Open labeled case series
- 2.5 mg of Letrozole / 2.5 mg of norethisterone acetate
- Followed at 1, 3, 6, 12 months
- Dysmenorrhea, Dyspareunia and Pelvic Pain assessed using visual analog scale
- Quality of life assessed with Short Form Health Survey
- 5 patient underwent repeat surgery


Endometriosis Pain (Visual Analog Scale)

At completion of study all participants had improvement in:

- physical role limitations ($P<0.025$)
- social functioning ($P<0.025$)
- emotional role limitations ($P<0.025$)
- mental health ($P<0.025$)

Refractory Endometriosis

- 16 patient with CPP
  - 16 L/S
  - 16 OCPS
  - 10 Lupron
  - letrozole 2.5 + aygestin 2.5 mg
  - Mean 180 days
  - Follow up 513 days

Abushahin, Fert Steril Oct 2011

Endometriosis

- Bladder
  - Improved symptoms
  - Limited by side effects


- Ovarian Endometriomas
  - Reduced size
  - Improved symptoms
  - No change in BMD after 6 months


Endometriosis and Infertility: Tubal Occlusion
Surgical Treatment

- Two large, multi-center, randomized control trials to determine if laparoscopic treatment of mild/moderate endometriosis improved fertility.
- Laparoscopic resection/ablation vs. diagnostic laparoscopy

Canadian trial (1997)†

- 341 women aged 20-39 with 12 mo history of infertility and no previous surgical treatment of endometriosis.
- In treatment group, all visible lesions destroyed and adhesions lysed.
- Follow up for 36 wks post operatively for pregnancy.

Canadian Trial (cont)

- 30% of patients were found to have stage II endometriosis
- Pregnancy at 36 wk
  - Operative group – 30.7%
  - Diagnostic group – 17.7%
- Fecundity rates
  - Operative group – 4.7
  - Diagnostic group – 2.4
Canadian Trial (cont)

- Monthly fecundity rates in patients undergoing surgery lower than the rate expected in fertile women (comparable to unexplained infertility)
- 1 in 8 women with minimal/mild endometriosis would benefit from resection or ablation of endometriosis.

Italian Trial (1999)

- 101 women, <36 years with a 2 year history of infertility, no previous laparoscopic diagnosis of endometriosis (60% Stage II)
- Followed for 1 year postoperatively for pregnancy
- Pregnancy at 12 months
  - Operative group – 24%
  - Diagnostic group – 29%
  - Not statistically significant
Comparing trials

- 341 women vs. 101 women
- 30% with stage II endometriosis vs. 60% with stage II endometriosis
- The odds ratio for pregnancy with surgery when combining the two studies is 1.7

Surgery Helps with IVF success???

- Littman et al, Fertility and Sterility, December 2005
  - Study showed 76% pregnancy rate following surgery in patients with IVF failure versus 37% in controls
  - However denominator is 29 patients . . . .

Endometriosis: Efficacy of Treatments AFTER surgery

<table>
<thead>
<tr>
<th>Cycles of treatment</th>
<th>% Pregnant</th>
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<tbody>
<tr>
<td></td>
<td>IVF</td>
</tr>
<tr>
<td></td>
<td>FSH/IUI</td>
</tr>
<tr>
<td></td>
<td>CC/IUI</td>
</tr>
<tr>
<td></td>
<td>Coitus</td>
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</tbody>
</table>

Plot showing% Pregnant vs Cycles of treatment for IVF, FSH/IUI, CC/IUI, and Coitus.
Treatments for Endometriosis: FSH Shots & IUI versus IVF

Cumulative Pregnancy rate (%)

Cycle number

- IVF
- FSH/IUI

Endometriosis and Fertility Treatment

- Surgical Treatment appears to enhance pregnancy rate. NNT = 12 (40)
- No clear benefit of pre-treatment medical therapy
- No clear impact of endometriosis on IUI, IVF or donor egg cycles
- Advanced stage disease appears to be more responsive to long term suppression prior to IVF.

Endometriomas: Surgical Treatment

- No effect
  Olivier, 1995
- Prior resection vs. current endometrioma (>3cm)
  - No diff in implantation, miscarriage or pregnancy rate
  Garcia-Velasco, 2004
- Poor prognosis
  - Lower oocyte number
  Yanushpolsky, 1989
  - Higher SAB rate
- Contralateral ovary as control
  - Lower response to stimulation (follicle and egg #)
  Somigliana, 2006
**Endometriomas: Surgical Treatment**

- Aspiration prior to ART resulted in higher E2 but no difference in # of oocytes or pregnancy rate
  - Pabuccu et al. F&S, 1998
- Removal of cyst wall superior to drainage with bipolar coagulation
  - Better pain relief
  - Lower recurrence rate
  - Higher Spontaneous pregnancy rate (6/9 vs. 4/7)
  - Beretta, F&S, 1998

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**Laparoscopic vs. Robotic Surgery**

<table>
<thead>
<tr>
<th>Stage of endometriosis</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robotic</td>
<td>14</td>
<td>17</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Non-Robotic</td>
<td>14</td>
<td>16</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th></th>
<th>RAL (n = 40)</th>
<th>SL (n = 38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean operative(min) (range)</td>
<td>191 (135-295)</td>
<td>159 (85-320)</td>
<td>0.045</td>
</tr>
<tr>
<td>Mean blood loss ml (range)</td>
<td>60 (0-350)</td>
<td>65 (0-500)</td>
<td>0.823</td>
</tr>
<tr>
<td>Intraoperative and postoperative complications</td>
<td>0</td>
<td>0</td>
<td>n/a</td>
</tr>
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Nezhat, C. Fertil Steril. 2010 Dec;94(7):2758-60

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**Laparo-endoscopic single site (LESS) surgery and single site robotic surgery**

AAGL 2013 Position Statement

"To date, there are no studies showing the differences in outcomes for endometriosis and course of the disease between robotic-assisted and conventional laparoscopic surgery."

Assisted Reproductive Technologies

• With surgically treated endometriosis, clomid timed IUI shown to increase cycle fecundity

• Plateau of fecundity after 3-4 cycles of clomid timed IUI

• IVF-ET has higher first-cycle fecundity than cumulative fecundity after six clomid timed IUI cycles

ART (cont)

• Surgery before IVF may increase pregnancy rate.

• GnRH agonist for 3mo before controlled IVF-ET may result in higher pregnancy rates
  • Suppresses IL-1 and TNF alpha
  • May have beneficial effect on NK cell
ART (cont)

Study comparing IVF patients with endometriosis (I-IV) with tubal factor infertility

• Comparable implantation rates between I/II and III/IV
• Implantation and pregnancy outcome not affected by presence of endometriosis

Conclusion

• In pts with infertility, think about endometriosis
• In pts with endometriosis associated infertility, treat early
• Hormonal suppression key
• Laparoscopy is the only modality that addresses infertility and pelvic pain
• Robotic approach may be of benefit in advance stage disease

Conclusion

• NSAIDS
• OCPs
• Progestins
• Aromatase Inhibitors
• GnRH analogs with add back
• Antidepressants
• Multidisciplinary Pain Management