

# **MEDICAL MANAGEMENT OF ENDOMETRIOSIS**

**Betty Anne Johnson, M.D., Ph.D.**

**Professor of Medicine**

**Director, University Student Health Services**

**March, 2001**

## **1. General Considerations:**

- Common:
  - Affects 71% of women with pelvic pain
  - Affects 84% of women with infertility and pelvic pain
  - Confirmed histologically on 45-50% of asymptomatic women at laparoscopy

## **2. Pathogenesis**

- Endometrial tissue implants in extrauterine locations, listed in decreasing frequency:
  - Ovaries
  - Anterior and posterior cul-de-sac
  - Posterior surface of the broad ligament
  - Uterosacral ligaments
  - Fallopian tubes
  - Sigmoid colon
  - Appendix
  - Round ligaments

## **3. Clinical Presentation:**

- Most patients are asymptomatic
- Size of lesions does not correlate with the severity of the disease
- Classic triad: dysmenorrhea, dyspareunia, and infertility
- Dyspareunia is usually associated with implants on the uterosacral ligaments, deep pelvic implants, lesions of the rectovaginal septum, or a fixed retroverted uterus
- Infertility: no direct cause has been identified unless the woman has anatomic distortion and fibrosis of the pelvis. Nonetheless, endometriosis occurs more frequently in women with infertility than in normal fertile women undergoing laparoscopy.

#### 4. **Lesions:**

- Clear vesicles in the early stages
- Red, blue or brown lesions
- Multiple filmy and dense adhesions from the ovary to the pelvic sidewall or to the uterus or posterior cul-de-sac
- Dark red fluid cysts
- Cyst cavities of endometriomas

5. **Medical Treatment:** goal is to induce either a pseudopregnancy (oral contraceptives, progestins) or a menopausal state (gonadotropin-releasing hormone [GnRH] analogue) state to inhibit or delay progression.

- Oral contraceptives:

- use in conjunction with NSAIDs for initial management in the woman who does not desire fertility
- progestational agent impedes the effect of estrogen on the endometrial lining and induces decidualization and subsequent atrophy of existing endometriotic lesions
- if failure after 3 months, go to a more aggressive approach. Switching OCPs will not work

- Progestins:

- Mechanism same as above. At high doses, progestins will also inhibit gonadotropin secretion and ovarian hormone production, inducing an amenorrheic state.
- Side effects: weight gain, fluid retention, HA, depression
- Can use oral medroxyprogesterone acetate, 50 mg daily, which has improved sx in 80% of pts with moderate to severe endometriosis. 30% had dysfunctional uterine bleeding on this regimen.
- Other regimens:
  - Medroxyprogesterone acetate 30 mg po daily (recurrence rates higher than above regimen after 2 years of treatment)
  - Norethindrone acetate, 5 mg po daily for 6 months
  - Megestrol acetate 40 mg po daily for 6 months
  - Parenteral medroxyprogesterone acetate depot given at 100 mg q 2 weeks for 3 months followed by 200 mg monthly for 3-6 months

- Danazol:
  - Synthetic derivative of 17alpha-ethinyltestosterone
  - Directly inhibits steroidogenic enzymes, endometriotic implant growth, and pituitary gonadotropin secretion
  - Decreases sex hormone-binding globulin (SHBG) resulting in increased free testosterone levels which cause acne and hirsutism
  - Other side effects: weight gain, hot flushes, mood changes, depression, muscle cramps, decreased breast size, decreased HDL, increased LFT's. On average, pts gain 10 lbs during the course of treatment, have a 50% decrease in HDL and a concomitant increase in LDL. 85% of pts experience bothersome side-effects and 10% discontinue therapy.
  - 80% experience relief or improvement in pain within 2 months of starting treatment
  - Recurrence after treatment approaches 50% by 4-12 months after discontinuation
  - Danazol is given po in divided doses ranging from 400 to 800 mg daily for 6 months. No advantage of the 800 mg over the 400 mg.
  - No increase in fertility shown
  - Should use another method of contraception as androgenic action may prove detrimental to the developing fetus should conception occur
  
- Danazol vaginal rings:
  - 88% of those with deep endometriosis had a decrease in dysmenorrhea and 92% had a decrease in tenderness of the cul-de-sac within 3 months of use. Effective in treating severe endometriosis without the androgenic side effects.
  
- Gonadotropin-Releasing Hormone Agonists:
  - Most predictable form of medical therapy
  - Bind to receptors in the pituitary gland, initially resulting in a release of FSH and LH, followed by modulation, a decrease in gonadotropin secretion, and eventually cessation of production of estrogen by the ovaries
  - Overall comparable or more effective than danazol
  - Results in improvement or resolution of pain sx in all stages of disease
  - Recurrence rate of 57% within 6 months of discontinuation; more severe cases more likely to recur
  - Usual dose

- nasal nafarelin 400 to 800 micrograms daily
  - subcutaneous goserelin 3.6 mg monthly
  - intramuscular leuprolide 3.75 mg monthly
- Side effects of hypoestrogenic state may be severe: vaginal dryness, hot flushes, insomnia, depression, libido changes, HA, and fatigue. May have 6% decrease in trabecular bone by 6 months (largely reversible). Do not experience the androgenic side-effects of danazol
  - Add-back therapy has gained wide acceptance...ultimate goal is to decrease vasomotor sx and the detrimental effects on bone density
  - 100 mg daily add-back medroxyprogesterone acetate reduces vasomotor sx and bone density loss
  - norethindrone at 1.7 mg suppresses vasomotor sx
  - higher doses of norethindrone spare bone losses
  - transdermal 17 beta-estradiol or conjugated equine estrogens administered with medroxyprogesterone acetate decreases vasomotor sx and bone loss without increases in pain

#### 6. **Surgical Treatment:**

- No longer considered first-line
- Consider for those who fail medical therapy
- Specificity of laparoscopic dx ranges from 40-80% depending on the knowledge and skill of the surgeon so complete excision or ablation is often technically difficult

#### 7. **Future Treatment:**

- Medicated vaginal rings
- Inhibitors of steroidogenic enzymes
- GnRH antagonists

#### 8. **References:**

Minjarez DA, Schlaff WD. Update on the medical treatment of endometriosis. *Obstetrics and Gynecology Clinics of North America*, 2000;27:641-651.