GU Endometriosis

Grand Rounds VGH
May 11, 2005
Omar Nazif

Outline

• Case Presentation
  - Hx, Px, Imaging
• Review of Endometriosis
  - Def’n, Etio, Epid, Pathology, Pathophysiology, Staging, Imaging, Dx, Medical and Surg Mgt
• Case Presentation
  - Mgt
• Summary
Case Presentation

• **ID**
  - 25 yo F, healthy, assessed in mid Sept 2004

• **RFR**
  - Bilateral hydroureteronephrosis

• **HPI**
  - Intermittent abd pain for several days
  - Perivaginal bleeding x 1 mo
  - Menorrhagia – 7 pads / day
  - Menses 4-5 days
  - Cyclic pelvic pain
  - No LUTS

• **Meds**
  - Alesse BCP
  - Zelnorm

• **PUHx / PMHx**
  - IBS
  - PAP N
Case Presentation

• **Px**
  - **Abd**
    - Benign
    - DRE N
  - **Pelvic exam**
    - Bulky uterus
    - Full adnexa
    - Nodularity of posterior cul-de-sac
    - Blood @ cervical os

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Case Presentation

• **Tests**
  - CBC N
  - Lytes N
  - Cr elevated @ 102
  - U/A +ve for nitrites
  - U C&S -ve
Case Presentation

**Imaging in ER**
- US abd / pelvis
- US transvaginal
  - Hydroureteronephrosis 5 cm from UVJ
  - No pelvic masses
  - Cystic / solid L ovary

Case Presentation

**Imaging**
- CTKUB ? urolithiasis
  - Bulky uterus
  - Full adnexa
  - Mod bilat hydroureteronephrosis
  - No stones
  - ? Pelvic mass
**Case Presentation**

- **Impression**
  - Bilat hydroureteronephrosis NYD

- **Plan**
  - CT IVP
  - Endometrial Bx per Gyne
  - Potential for laparoscopy by Gyne dependant on results
  - Consider C&P

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**CT IVP**

- September 2004
CT IVP Findings

- Bilateral hydroureteronephrosis 5 cm UVJ
- Stranding and fibrous reaction around uterus and left ovary
- Trace free fluid in pelvis
- No LAD
- Cannot exclude tumor or infection
Approach to Ureteral Obst’n

- **Luminal**
  - Neoplastic, stone, clot, papilla, fungus, infection

- **Intramural**
  - tumor, stricture, TB, endometriosis, traumatic

- **Extra-luminal**
  - Gyne - infection, cysts, endometriosis, neoplasm
  - GI - colon/SB neoplasm, IBD, diverticular D
  - Other - ligation, injury, RPF, pelvic lipomatosis, XRT
  - LAD, aneurysm, vascular graft

Retrograde Pyelogram

- September 2004
Case Presentation

- **C&P + Stents Sept 2004**
  - 4 cm narrowing of ureter bilaterally
  - Hydroureter and hydronephrosis bilat to level of narrowing
  - Placement of bilat JJ stents
Retrograde Pyelogram

• January 2005 with JJ stent change
C&P Findings

- Ongoing bilateral hydronephrosis
- Dilation of ureters down to lower edge of SI joint
- Stents changed
- Bladder capacity 800 cc

Case Presentation

- Diagnostic Laparoscopy Oct 2004 Gyne
  - Extensive adhesions
  - Evidence of endometriosis
  - Obliterated posterior cul-de-sac
  - Large bowel adherent to uterus & R adnexa
  - Fallopian tubes not identified d/t adhesions
  - Disease confined to pelvis
**Endometriosis Definition**

- The presence of endometrial glands and stroma ± inflammatory cells or hemosiderin-laden mø’s outside uterus
- Formerly endometriosis externa

**Adenomyosis Definition**

- Separate entity
- Endometrial tissue w/in wall of uterus
- Can coexist w endometriosis, but no strong correlation
- Formerly endometriosis interna
Urological Context

• Pt’s presenting w bladder pelvic pain and bladder complaints
• Pt’s presenting w complications of endometriosis
  - Hematuria
  - Ureteral obst’n
• Most serious urologic complication is ureteral involvement

Location of Endometriosis

• Most commonly found in pelvis
  - Ovaries
  - Posterior cul-de-sac
  - Uterosacral ligaments
  - Posterior broad ligament
  - Anterior cul-de-sac
Location of Endometriosis

- Less commonly found
  - Uterine serosa
  - Rectovaginal septum
  - Cx
  - Vagina
  - Rectosigmoid
Rare Location of Endometriosis

- GU
  - Bladder (84%)
  - Ureters (15%)
  - Kidney (10 case reports)
  - Urethra (2 case reports)
- GI
  - Ileum, appendix, cecum, umbilicus
- Distant sites
  - Lungs
  - Other

Epidemiology

- True prevalence unknown
- 1-5% of F in reproductive years
- 30% of infertile F
- 15-71% of F w chronic pelvic pain
- <5% of F postmenopausal
- GU endometriosis is rare
- All races equal
Genetics

• Familial incidence
• Polygenic / multifactorial mech’n has been documented
• F w affected 1st degree relative
  – 10x incr risk of D

Risk Factors

• Nulliparity
• FHx of endometriosis
• Short menstrual cycles
  – < 27 days
• Prolonged flow
  – > 8 days
• Partial or complete obst’n of menstrual flow
  – Vaginal septa
  – Tight cervical os
Etiologic Theories

1. Metastasis of endometrial tissue to ectopic loc’n
   - Menstrual implantation
   - Intraoperative implantation
   - Lymphatic / vascular spread

2. Metaplastic development of endometrial tissue at ectopic site (metaplastic theory)
   - Pelvic endometriosis by process of metaplasia from pelvic peritoneum c/w Mullerian potential of tissue

Metastatic Theory

• Sampson’s Theory
  - Retrograde menstruation results in sloughed endometrial tissue & steroid sensitive cells are fluxed thru Fallopian tubes → implantation outside of uterus
Metastatic Theory

- Supported by following observations
  - Lesions are m/c in regions near tubal ostia
  - Lesions occur in dist’n c/w uterine position
  - Endometriosis is more common in F w
    - Early menarche and heavy menstrual flow
    - Long menses > 7 days
    - Congenital obst’n to menstrual flow
    - Freq menses T < 27 days

Metaplastic Theory

- Metaplastic differentiation of serosal surfaces
  - Coelomic epith
  - Mullerian remnant tissue
- Both endometrial and peritoneal cells derive from coelomic wall epith
Metaplastic Theory

• Supported by
  - Presence of endometriosis in F where metastasis would not occur
    ▪ Turner’s Syndrome
    ▪ Pure gonadal dysgenesis
    ▪ Pt’s who are amenorrheic, hypoplastic uterus, or uterine agenesis
  - M pt’s on E2 Tx for CaP
Etiology

• F < 17 yo
  – Obstructive Mullerian duct anomalies
    • Cx
    • Vagina

• Postmenopausal F
  – ? Related to HRT
  – Rare

• M
  – Undergoing long-term E2 Tx for CaP

Immunology

• F w endometriosis have been found to have abN
  – T-cell mediated cytotoxicity
  – NK cell activity
  – B cell fn
  – Complement deposition

• Growth factors
Staging of Endometriosis

- Most accepted staging is by American Society of Reproductive Medicine (ASRM) 1996
  - Stage I
    - Minimal
  - Stage II
    - Mild
  - Stage III
    - Moderate
  - Stage IV
    - Severe

Table 2: Endometriosis Staging System of the American Fertility Society

<table>
<thead>
<tr>
<th>Location</th>
<th>Depth of Penetration</th>
<th>Size</th>
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<tbody>
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<td></td>
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<td>&lt;1 cm</td>
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<tr>
<td></td>
<td>Deep</td>
<td>2</td>
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<tr>
<td>Ovary</td>
<td>Right superficial</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Right deep</td>
<td>4</td>
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<tr>
<td></td>
<td>Left superficial</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Left deep</td>
<td>3</td>
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</table>

B. Obliteration of the Posterior Cul-de-sac

<table>
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<tr>
<th>Degree of Obliteration</th>
<th>Score</th>
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<tr>
<td>Partial</td>
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<tr>
<td>Complete</td>
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C. Adhesions

<table>
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<th>Appearance</th>
<th>Amount of Surface Involvement</th>
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<td>&lt;1/3</td>
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<td>Ovary</td>
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<td></td>
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<td></td>
<td>Left dense</td>
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</tr>
</tbody>
</table>

Note: — Stage I (minimal) = score 1-5, stage II (mild) = score 6-15, stage III (moderate) = score 16-40, stage IV (severe) = score >40. From reference 36.
Staging

• Critics
  - Stage of D does not necessarily correlate with severity of Sx or prognosis for fertility
  - No consistent Tx regimens based on stage

• Benefits
  - May offer standardization in assessing response to Tx

Pathophysiology

• Ectopic endometrial deposits are dependent on cyclic hormonal stimulation
  - Regress in pregnancy
  - Involute completely in menopause
  ▪ Surgical or physiological

• After regression of deposits, the resulting adhesions, fibrosis, & scarring remain
Pathology

• **Gross**
  - Implants vary from punctate foci to small stellate patches typ < 2 cm
  - Pigment incr w age of lesion
    - Initially: white, yellow, or red
    - Mature: blue, brown, black
  - “Powder burns”
    - Brown ecchymotic lesions
  - Implants change in appearance related to menstrual cycle
Pathology

- **Endometriomas**
  - Endometriotic cysts
  - Typ occur in ovaries
  - d/t repeated cyclic hemorrhage w/in implant
  - “chocolate cyst”
Pathology - Microscopy

- **Endometriosis** is composed of:
  - Endometrial glands
  - Stroma
  - Occasional smooth muscle fibers

- **Inflammatory response**
  - Induced by hemorrhage within foci
  - Histiocytes laden with hemosiderin and lipofuscin
Presentation

- **Classic triad 40%**
  - Dysmenorrhea
  - Dyspareunia
  - Infertility
- ~30% of F w chronic pelvic pain have endometriosis
General SSx

- Pelvic pain
- Infertility
- Rectal discomfort
- Back pain
- Menses cycle < 27 days
- Prolonged menses > 8 days
- Improv’t of Sx during pregnancy

General SSx

- Dysmenorrhea
  - Primary vs secondary
  - Pain prior to onset of menses
  - Starting yrs after relatively pain free menses
- Dyspareunia
  - Deep penetrating
  - Typ worse in premenstrual phase
- Sacral backache
  - assoc w menses
GU SSx

- Urgency
- Frequency
- Suprapubic pain
- Vague flank pain
- Renal colic
- Cyclical pain worse @ time of menses

GI SSx

- Catamenial diarrhea
- Rectal bleeding
- Constipation
Pulmonary SSx

- Pleuritic CP
- PTX
- Pleural effusions
- Cyclic hemoptysis

CNS SSx

- Cyclic HA’s
- Sz’s
- SAH
Derm SSx

- Catamenial cutaneous bleeding
- Tenderness

General Physical Exam

- In general, findings non specific
- Perform exam during early menses when implants will be large and tender
Pelvic Exam

- Thickened or nodular rectovaginal masses
- Adnexal tenderness if ovarian involvement
- Fixed pelvic organs from adhesions
- Localized tenderness on
  - Uterosacral ligaments
  - Cul-de-sac
- Uterus fixed in retroverted pos’n

Diagnosis

- Based on
  - Hx
  - Px
  - Imaging
    - Laparoscopy w Bx
- Gold Std is laparoscopy with Bx
Vesical Endometriosis SSx

- Menstrual hematuria
- Suprapubic P
- LUTS
  - Freq, urgency, dysuria
- Sx’s present in 75% of pt’s
- Cyclical symptomatology
  - Pain worse @ menses

Vesical Endometriosis DDx

- IC
- CIS of bladder
- Recurrent cystitis
**Vesical Endometriosis**

- **Cystoscopy + Bx**
  - Endometriomas will appear edematous, bluish, submucosal cystic lesion
  - Bladder base behind trigone
  - Dome of bladder
  - Mucosa is typ intact
  - Cystic lesions may rupture into bladder → ulcerative lesion

**Vesical Endometriosis Dx**

- **Definitive Dx histology**
- **Cold cut Bx**
- **Loop resection**
- Requires high index of suspicion
Ureteral Endometriosis

• **Classification**
  - **Intrinsic**
    - Foci w/in muscular coat
    - Can mimic polypoid ureteral tumor
  - **Extrinsic**
    - Periureteral fibrosis
    - Ureteral obst’n

• **The most serious urologic complication of endometriosis**

Ureteral Endometriosis SSx

• **Pathognomonic**
  - Cyclic flank pain w/ hematuria - rare 15%
• **Vague flank pain**
• **Pelvic pain**
• **LUTS**
• **Delayed Dx is common**
  - assoc w permanent renal damage
• **Often presents w mild & non specific Sx**
**Ureteral Endometriosis Px**

- Perform Px during early menses
  - Lesions larger & more tender d/t vascular congestion
- Tender nodules
  - posterior vaginal fornix - bimanual
  - uterosacral lig’s & cul-de-sac - rectovaginal
- Fixed uterus & asymmetric adnexa

- **+ve physical exam in 100% pt’s w bilat D**
  - 60% w unilateral ureteral obst’n

**Ureteral Endometriosis**

- Consider Dx in any premenopausal F w ureteric obst’n of unknown etio

- 10% of cases bilateral

- Both ureters involved equally
Imaging Endometriosis

- Multiple modalities

Imaging - US

- Accepted as initial screening modality of choice
- Ovarian endometriomas
- Transvaginal US
  - Sensitivity 97%
- Abdominal US
  - Sensitivity 80%
- Perform both
Imaging - US

• Ovarian endometriomas
  - large cysts
  - low level homogenous internal echoes
  - echogenic wall foci
Imaging - MRI

- Best imaging modality
- Endometriotic cysts
  - High signal intensity T1
  - Shading on T2 images
- Often used for problem solving
**Imaging - Less Accurate**

- CT
  - May be helpful for GU complications
- Colonoscopy
- Barium enema

**Imaging - IVP & C&P**

- IVP and ureteral endometriosis
  - Non specific
  - resembling stricture or tumor
  - Strictures typ 2-5 cm cephalad to UVJ

- Retrograde Pyelogram
Laparoscopy

- Endometrial lesions have many appearances
  - Red
  - White
  - Non pigmented
  - Blue
  - Brown
  - Black
Open Surgery
Special Tests

- **CA-125**
  - Mullerian Ag
  - Will be elevated in ~40% of pt’s w Stage III or IV endometriosis
  - Not v sensitive
  - Wide DDx
### Conditions Associated with an Elevated Serum CA 125 Concentration¹

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<td>Fallopian tube cancers and germ cell tumors</td>
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<td>Ovarian hyperstimulation</td>
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<tr>
<td>Pelvic inflammation</td>
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¹Adapted from Gallup, DG, Talledo, OE, South Med J 1997; 90:972.

### Management

- Depends on pt presentation
  - Pelvic pain vs
  - Infertility

- Rationale for medical Tx
  - Abolish hormonal stimulation
  - Induce amenorrhea
Pelvic Pain Mgt

• **Central dogma**
  - Interventions that decr E2 prod’n and action OR increase androgen action will be effective in Tx of chronic pelvic pain

• **Modalities**
  - NSAIDs
  - E2-P4 regimens
  - GnRH agonists
  - Androgens

NSAI Ds

• **1ST line Tx**
  - Ibuprofen
    - 600 mg po QID
  - *Naproxen*

• **NSAI Ds do not**
  - Shrink endometrial implants
  - Prevent growth of implants

• **Pain returns after Rx stopped**
BCP

• **MOA**
  - Suppresses FSH, LH, and endogenous E2 prod’n
  - Causes decidualization and atrophy of endometrial ectopic tissue

• **Efficacy**
  - Relief of mild to mod pain
  - Less effective than GnRHa and Danazol
  - Can slow progression of D

BCP

• **Dosing**
  - Administer cyclically or continuously
  - Continuous helps dysmenorrhea
Danazol

- **History**
  - Old compound 1971
  - Derivative of 17 alpha ethinyl testosterone

- **MOA**
  - Creates androgenic / low E2 environment → atrophy of endometrial implants
  - Suppresses midcycle LH and FSH surge
  - Inhibits ovulation
  - Decrease ovarian steroidogenesis

Danazol

- **Side Effects (common)**
  - Decr hDL
  - Incr AST & ALT
  - Incr wt
  - Decr breast size
  - Other androgenic changes: acne, hirsutism, deepening of voice, HA, hot flashes . . .
Danazol

- **Efficacy**
  - Improv’t in 90%
  - Good for resolving implants in mild – mod D
  - Large endometriotic cysts do not respond well
  - Many D/C Rx b/c of S.E.’s
  - Sx recur after Tx stopped

- **Dose**
  - 200-400 mg BID – QID for 6 mos or more

GnRHa

- **Typical drugs**
  - Naferelin (pn), leuprolide (im), goserilin (sc)
  - Tx typ started after surgical Dx w Bx

- **MOA**
  - Induces hypogonadotropic hypogonadism
    - Downregulation and desensitization of pituitary
  - Decr in LH and FSH
  - Ovarian steroidogenesis drops to menopausal levels
  - Shrinks implants
  - Initial “flash” period of stimulat’n for 2 wks prior to hypoE2 state
GnRHa

- **Time to onset**
  - Pain relieved by 2nd or 3rd month
  - More effective than BCP for dyspareunia

- **Side Effects**
  - Decr bone density (2-7% loss)
  - Hot flashes, vaginal dryness, decr libido
  - HA
  - Depression

- **Duration of Tx**
  - Typ 6 mos

GnRHa

- **Dose**
  - Nafarelin 400-800 mcg nasal spray od
  - Goserelin 3.6 mg sc q 1 mo
  - Leuprolide 3.75 mg im q 1 mo
  - * menses typ return 60-90 days after cessat’n of leuprolide

- **Consider add-back Tx**
  - E2, P4 (norethindrone, conjugated E2)
  - Bone strengthening Rx
    - Bisphosphonates
    - PTH
    - Calcitonin
    - CaCO3
Progestins

• **Drugs**
  - Medroxyprogesterone acetate
  - Norethindrone acetate
  - Norgestrel acetate

• **Indication**
  - Inadequate response from BCP

Progestins

• **MOA**
  - Inhibition of endometriotic tissue growth
  - Causes decidualization
  - Eventual atrophy of endometrial tissue

• **Efficacy**
  - More powerful than BCP
  - 80% have partial or complete relief of pain
Progestins

• **Side Effects** (more common than BCP)
  - Bloating
  - Wt gain
  - Irreg uterine bleeding
  - Worsened depression
  - Amenorrhea for mos after Tx stopped

• Not recommended for F planning pregnancy

Progestins

• **Dose**
  - Medroxyprogesterone acetate 10 mg po TID or depot w 100-150 mg im q 1 mo
  - Norethindrone acetate 5 mg po od
Aromatase Inhibitors

• MOA
  - Regulates local E2 format’n in endometriotic lesions
  - Interrupts following p-way
    • PGE2 → incr aromatase expression & activity →
      local prod’n of E2 → +ve feedback cycle

• Currently investigational

Surgery

• Indications
  - Severe Sx
  - Failed medical Tx
  - Advanced D
  - Anatomic distortion of pelvic organs
    • Urinary tract obst’n
    • GI tract obst’n
  - Endometriotic cysts
Conservative Surgery

- Laparoscopy
- Often initial diagnostic procedure
- Excision, fulguration, laser vaporization of endometriotic implants

Definitive Surgery

- **Indications**
  - High stage D
  - Future pregnancy is not desired
- **Procedure**
  - Hysterectomy
  - Oophorectomy if ovaries damaged by D or menopause is approaching or no further fertility
Laparoscopy

• **Indications**
  - Pelvic Pain
  - Infertility
  - Mass
  - Diagnostic
• Most recommend Tx of adhesions, or large endometriomas (> 2 cm) w surgical intervention

Pelvic Mass

• **DDx**
  - Endometrioma
  - Chocolate cyst
  - Adhesions
  - Mass unrelated to endometriosis
• **Mgt**
  - Surgery for Dx and removal of mass
  - Medical Tx ineffective
Infertility

• Endometriosis may decr probability of pregnancy
• Distortion of N pelvic anatomy of ovaries and Fallopian tubes
• Many F conceive w/in 3 yrs
• Pregnancy rates better after surgery
  - Surgery more effective than hormonal Tx w mod or severe D

Infertility

• After conception no higher risk of complications

• Mgt
  – Surgery lysis of adhesions
  – Clomiphene
  – IVF
  • Best Tx for F w severe D and extensive scarring
Vesical Endometriosis

- Pt’s desiring fertility
  - Start w medical Tx
- Consider partial cystectomy
  - Partic in pt’s wanting to preserve fertility
  - Consider Rx for residual small foci
- Oophorectomy
  - In pt’s w no desire for fertility
  - Provided no ureteral involvement
- TAH BSO
  - High stage D w large bladder lesion

Ureteral Endometriosis

- Medical Tx
  - Rx may relieve Sx’s, rarely relieves periureteral scar & fibrosis
  - Rarely stops progression of ureteral obst’n
Ureteral Endometriosis

- Surgical approaches
  - Nephrectomy
  - Ureterolysis
  - Ureteroneocystostomy
  - Psoas hitch
  - Boari flap
  - Ileal interposition

Ureteral Endometriosis

- If no further fertility wanted
  - Resection of endometriosis
  - Bilat oophorectomy ± hysterectomy
  - Ureterolysis
  - Resection of involved segment
  - Ureteroneocystostomy orUU
  - Post op hormonal Tx
Ureteral Endometriosis

- Patients wanting to preserve fertility are unique challenge
  - Unilateral oophorectomy
  - Removal of endometrioma
  - Ureterolysis

Prevention of Endometriosis

- Nothing proven

- Reduce # & volume of menstrual cycles
  - BCP for several yrs
  - Multiple pregnancies
Prognosis GU Endometriosis

• **Vesical endometriosis**
  - Six cases of malig transformation
  - Ensure good f/u

• **Ureteral endometriosis**
  - Permanent loss of renal fn in 35% pt’s
  - Ensure regular renal evaluat’n
  - Ureteroneocystostomy & ureterolysis have similar outcomes

Case Presentation

• 6 mos later, no improv’t of hydrenephrosis
• Following laparoscopy, medical Tx started
  - Lupron
  - NSAIDs
• Ongoing pelvic pain despite Rx
• Pt wanting surgical Tx and fertility
Retrograde Pyelogram

- April 2005
Case Presentation

- Combined Gyne / Urology open OR

- **Operative Findings**
  - Obliterated cul-de-sac
  - Extensive adhesions around pelvic organs
  - Extensive fibrosis of ureters deep in pelvis
    - Thickened and diseased ureteral walls; R > L

Case Presentation

- **Procedure**
  - Midline abdominal incision
  - Ureters isolated at common iliacs
  - Ureterolysis
  - Dissection down to fibrosed pelvis
  - Bivalved bladder
  - Reimplantation of ureters bilaterally into bicornuate bladder

- Post Op cystogram N
- 6 wks later pt voiding well
Summary

- Endometriosis is an imp’t Gyne disorder affecting F in reproductive years
- Pathologically, it is d/t functional endometrium outside the uterus
- Physical manifestations are variable
  - Infertility
  - Dysmenorrhea
  - Pelvic pain
- Sx don’t necessarily correspond with degree of D

Summary

- Ovaries m/c site
- GU complications are rare
- Initial imaging US
- Definitive imaging w MRI
- Diagnosis by laparoscopy and Bx
- Mild – Mod Sx → Medical Tx
- Severe Sx, infertility, and other complications Tx surgically