Endometriosis

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Case 1:

- 30 y/o F PMH Borderline personality disorder, anxiety, depression, presents with complaints of LLQ abdominal pain and palpable abdominal nodules. She reports having these nodules for a few years but are now enlarged and very painful. Her pain improves if she lies still or takes pain medications (Tylenol, ibuprofen, Norco).

- GYN Hx: G4P1031, only child born via emergency C/S due to preeclampsia 4 years ago. She has regular periods every 28-30 days, menstruation lasting 3 days. Her periods have been painful her entire life except for when she took Depot Provera and had a Mirena IUD from when she was 18 y/o - 22 y/o.

- Vitals:
  - T = 97.8 F
  - HR = 79
  - BP = 140/95
  - RR = 16
  - O2 saturation = 100% on RA
Case 1: continued...

Physical exam:
- HEENT, Cardiac, Pulmonary, Lymph, and extremity exam were normal
- Abdominal exam: Pain along her LLQ with rebound tenderness. She has 2 palpable subcutaneous nodules along midline and left side of her C/S scar measuring 3-4 cm, well circumscribed,

Labs:
- B-HCG, CBC, CMP, and UA were all normal

Imaging:
- CT abdomen/pelvis without contrast
- Abdominal ultrasound
Case 1: continued...

Read: Ill defined soft tissue density in anterior abdominal wall rectus muscle and subcutaneous tissue concerning for spontaneous hematoma
Case 1: Continued…
What is Endometriosis?

- Defined as Endometrial glands and stroma that occur outside the uterine cavity.
- Most commonly located in the pelvic peritoneum but can have multiple other sites including:
  - Bowel
  - Bladder
  - Pleural cavity
- Common Presentations include: Dysmenorrhea, Pain, Dyspareunia, and Infertility
Epidemiology

- **Prevalence of endometriosis ranges from 1-7% of population**
  - Based on 4 studies of asymptomatic women undergoing tubal ligation

- **In Symptomatic women, prevalence increases. Endometriosis was present in:**
  - 57% of women undergoing laparoscopic evaluation with endometriosis as preoperative indication
  - 21% of women undergoing surgery for other indications but whom complained of pre-operative pelvic pain
  - 8% of women who did not have endometriosis listed as possible cause of their preoperative pelvic pain

Etiology

1. **Sampson’s Theory of Retrograde Menstruation**
   - Refluxed menses flow retrograde out of fallopian tubes and into the peritoneum subsequently developing their own blood supply

2. **Lymphatic / Vascular Spread**
   - Supported by cases of endometriosis that developed in pleura or groin

3. **Coelomic Metaplasia**
   - Parietal peritoneum undergo metaplastic transformation to endometrial tissue
   - Supported by cases of premenstrual or postmenopausal endometriosis

4. **Induction Theory**
   - Hormonal or biological factor induces differentiation of tissue to endometrium.
Risk Factors

**Increased Risks:**
- Nulliparity
- Early Menses (before 11 y/o)
- Mullerian Abnormalities (lower tract obstructions)
- Heavy Menses
- Caucasian and Asian ethnicity

**Decreased Risks:**
- Multiple births and Breastfeeding
- African American and Hispanic ethnicity
- Late menarche (after 14 y/o)
- High Consumption of Omega 3 fatty acids

*There does appear to be familial inheritance but no gene has been identified!*
Symptoms and Causes?

- **Chronic Pain**
  - This may be cyclic or chronic
  - Typically related to affected area

- **Severe Dysmenorrhea**
  - Typically precedes menses by 24 hours
  - Does not typically respond to NSAIDS
  - More Severe than Primary Dysmenorrhea

- **Dyspareunia**
  - May begin after years of pain free intercourse
  - Often from rectovaginal / uterosacral ligament involvement

- **Infertility** - Incidence of 20-30%
Symptoms and Causes?

- Symptoms typically caused by production of inflammatory and pain mediators.

- Every month endometrial tissue, blood, and protein leak onto affected organs or peritoneum leading to production of Cytokines, Prostaglandins, and growth factors.

  **Prostaglandins cause:**
  - Contraction of smooth muscle which leads to “Uterine Cramping” and “bloating”
  - Nausea and Vomiting
  - Flu like symptoms (body aches, elevated temperature)
Diagnosis: Physical Exam

- Typically focused on the lower abdomen and pelvis
- Speculum exam
  - Need to evaluate for other causes including Vaginitis, Cervicitis, vaginal abnormalities
  - You may visualize endometriosis directly on exam or see nodular scarring
  - Lesions will tend to bleed and be tender on contact
- Bi-manual exam / Rectovaginal exam
  - Uterosacral ligament nodularity
  - Enlarged cystic adnexal mass
  - Retroverted and fixed uterus
- Exam is generally not sensitive for detecting disease
  - Nodularity may be more palpable during menses
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Diagnosis: Lab Tests

- **Routine Labs to rule out other causes**
  - B-HCG
  - CBC
  - UA and Urine culture
  - Gonorrhea/Chlamydia PCR
  - Affirm or Wet Prep

- **CA-125**
  - Sensitive for screening for peritoneal inflammation but NOT Specific

- **Other markers for detecting generalized inflammation but are not specific to Endometriosis:** CA-19-9, TNF-A, PP14
Diagnosis: Imaging

- Transvaginal Ultrasound
  - Mainstay in evaluating women with pelvic pain (no radiation and low cost)
  - Can help evaluate for other causes (ovarian cysts, masses, fibroids)
  - Very accurate in detecting endometrioma’s >2 cm and adenomyosis
Diagnosis: Imaging

- **CT Scan**
  - This is more helpful for bowel or bladder involvement (signs of obstruction)
  - Also useful for endometriosis outside of the pelvis

- **MRI**
  - Sensitivity and Specificity similar to TVUS
  - This can visualize adhesions and endometriomas
  - Typically more useful for surgical planning
  - Significant cost $$$
- CT pelvis showing ovarian endometrioma

- MRI pelvis showing endometrioma between uterus and bladder
Definitive Diagnosis: Surgical

- Laparoscopic exploration with biopsy is confirmatory
- 2 different appearances:
  1. Black / Blue lesions: pigmented due to hemosiderin deposition
  2. White / Red lesions: endometrial tissue
    1. These correlate better with diagnosis

- ASRM classification system
  - Stage 1 - Minimal (small lesions and no adhesions)
  - Stage 2 - Mild (superficial & deep implants, \(<5\) cm, no adhesions)
  - Stage 3 - Moderate (large lesions +/- adhesions)
  - Stage 4 - Severe (multiple large lesions with adhesions)
STAGES OF ENDOMETRIOSIS

Stage I, minimal

Stage II, mild

Stage III, moderate

Stage IV, severe
Counseling different treatment options depends on patient's goals and symptom severity

Mild - Moderate symptoms: (no absence from school/work and no large lesions seen on TVUS)
- Can be treated conservatively
  - NSAIDS, OCP's, GnRH agonist, new products being researched
  - Should be offered referral to GYN for possible Surgical intervention

Infertility or Severe Symptoms
- Motivated patients can choose GnRH agonists with add back therapy
- Surgical intervention w/wo medication
Treatment: Expectant Management

- Study by Sutton et al comparing 63 women with mild-moderate endometriosis who underwent laser therapy or expectant management. All underwent 2nd look laparoscopic evaluation 1 year later.

- **Findings for expectant management:**
  - 29% disease regression
  - 42% disease unchanged
  - 29% disease progression

- **Findings for surgical group:**
  - 90% had continued pain relief and disease regression after 1 year

- There are no trials for severe endometriosis as expectant management is not recommended.

**Treatment: NSAIDS**

- Often 1st line therapy for women with suspected Endometriosis and prior to Laparoscopic evaluation
- Primarily symptom relief
- Is not associated with disease regression
- Recommended that it be Non-selective Cox-1 and Cox-2 inhibitor
Treatment: Combined OCP’s

- Mainstay treatment for Endometriosis as it leads to decidualization.
- They have many benefits:
  - Decrease menstrual flow
  - Can decrease nerve fiber density and growth factor expression
  - Act as contraception and prevent ovulation
- No difference between Cyclic or Continuous on disease progression but **continuous will decrease pain** more effectively.
- Low dose is **not** superior to regular dosing and may lead to **more bleeding**.
Treatment: Progestin

- Antiproliferative effects causing initial decidualization and atrophy
- They have many benefits:
  - Have long acting formulary
  - Can be used when Estrogen is contraindicated
  - Decrease pain
  - Can decrease nerve fiber density and growth factor expression

- Formulary: Oral, Depo-Provera, Nexplanon, Mirena IUD, SPRM’s
Treatment: Progestins

- **MedroxyProgesterone:** Oral or Depot Shot
  - Increased dosage correlates with better pain control
    - Oral: 10-30 mg PO daily, some studies even going as high as 100 mg PO daily
    - Depot Provera: 150 mg IM every 3 months, some studies giving up to 300 mg every 3 months.
  - Side effects increase with increased dosage
    - Acne, Weight gain, irregular bleeding, edema, temporary bone loss with LT use

- **Norethidone Acetate:** synthetic oral progesterone
  - Initiate at 5 mg/day and increase by 2.5 mg/day until desired pain control. Max dose of 20 mg/day
  - No long acting formulary
  - Similar side effect profile.

Treatment: Progesterone

- **Mirena IUD**
  - Similar pain control when compared to GnRH agonists but with less side effects
  - ~50% continuation rate after 3 years due to intolerable side effects
  - May not be as helpful if there is endometriosis further outside the pelvis or affecting bowel / bladder.

- **Nexplanon / Implanon**
  - Only found case reports
  - Patients did report improvement of pain similar to Oral progestins
Treatment: Androgens

**Danazol**
- Directly inhibits GnRH secretion and steroidogenesis leading to hypoestrogenic state
- Requires high and frequent dosing (ex. 200-300 mg PO TID)
- Significant side effects: weight gain, nausea, hirsutism, hot flashes, atrophic vaginitis, etc.

**Gestrinone (only available in Europe)**
- Antiprogesterational agent
- Similar mechanism of action to Danazol but much better tolerated and at lower doses (ex. One tablet 3 x per week)
- No bone loss as compared to GnRH
Treatment: GnRH agonists

- **Normal Pituitary:** Goes through pulsatile release of GnRH stimulating ovarian steroidogenesis and ovulation with a negative feedback loop.
- **GnRH agonist:** Create non-pulsatile release and eventual desensitization of ovary to hormone.
- Leads to loss of estradiol production.
- Decreases Cox-2 receptors in patients with endometriosis.
- Only comes in injectable or intranasal forms.
  - **Lupron Depot**
    - Dosage: 3.75 mg monthly injection; 11.25 mg every 3 months
    - Cost: ~$1,500 - $5,000 per shot
  - **Nafarelin**
    - Dosage: 1 nasal spray BID
    - Cost: ~$500 per mL
Treatment: GnRH agonists

**Indications:**
- Often used prior to Laparoscopy and for severe cases
- Typically see pain relief after 3-6 months
- More effective for Dyspareunia than COCP’s
- Otherwise similar effect on pain control compared to COCP’s

**Side Effects**
- Insomnia, decreased libido, hot flashes, vaginal dryness, menopausal symptoms
- Bone loss: Significant after 6 months.
  - If used >6 months need “Add Back Therapy” with hormone replacement
  - Need regular DEXA scans if taking for >6-12 months
Treatment: On the Rise

- **GnRH Antagonists**
  - Work Immediately
  - Already being used for IVF but not approved for Endometriosis
  - No long term formulary, still needs Add Back Therapy

- **Aromatase Inhibitors**
  - Is being tested on Post-menopausal women with good studies so far

- **Progesterone Antagonists**
  - Only problem is it leads to unopposed estrogen

- **Selective Progesterone-Receptor Modulators (SPRM)**
  - Induce endometrial atrophy and amenorrhea
  - Improves pain
  - Still undergoing trials.
Case 2:

- 18 y/o African American F PMH Depression presents with complaint of worsening lower abdominal pain. She reports pain is aching and cramping in nature. Pain is constant but worsens with her periods. She reports pain improves with taking Motrin 800 mg tablets but does not completely resolve, denies aggravating factors. She denies fevers, N/V, diarrhea, dysuria, vaginal discharge. She comes today because pain is constant and is starting to prevent her from going to all of her college classes.

- **GYN Hx:** She is G0P0, first period when she was 10 y/o. Her periods are every 35-40 days, heavy bleeding lasting 5-7 days. She reports when she was 12 y/o that she missed 1-2 days of school every semester due to period pain but since then she has been dealing with it by taking NSAIDS. She has been sexually active in the past but no current relationships, did have some pelvic cramping after intercourse. She denies history of STD’s.

- **Social Hx:** She is in her first year of college and recently established care at your office. She lives in dorm room. She denies smoking or drug use.

- **Vitals:** Temp = 99.0F, HR = 72, BP = 95/60, RR = 12
Case 2: continued

- **Physical Exam:**
  - Cardiac and Pulmonary normal
  - Abdominal exam: NBS, tenderness to palpation over suprapubic and RLQ with rebound tenderness, Psoas sign and Rovsing’s sign negative.
  - Pelvic Exam: Normal vaginal mucosa, normal cervical os, normal physiologic discharge, no lesions
  - Bimanual Exam: Anteverted uterus, mild discomfort in RLQ, but no adnexal masses
Case 2: Continued

- B-HCG is Negative
- CBC - WBC = 9.2, Hgb = 11.2, Platelets = 185,000
- BMP is normal
- Gonorrhea / Chlamydia is negative
- Affirm is negative
- Urine Dip shows 1+ LE, negative nitrites, no blood
- Urine culture - mixed urogenital flora

**Transvaginal Ultrasound:** Endometrial thickness 7mm, no fibroids. Right ovary measures 3 x 2.9 x 2.1 cm, left ovary measures 2.6 x 2.5 x 2.9 cm. Follicles seen in both ovaries. Normal flow to ovaries bilaterally.
Case 3:

- 48 y/o F PMH current smoker, HTN, Obesity presents with complaints of painful periods with heavy bleeding. She has had this problem for a long time but now she is starting to also have some pain with intercourse which is why she is seeing you today. Pain with periods is 3/10 on pain scale, and pain with intercourse is 5/10. She denies any recent trauma, N/V, diarrhea, fevers, chills. She wants to know if there is anything that can relieve her painful periods or stop her periods.

- **GYN Hx:** G4P3013 all vaginal deliveries. Her first period was at age 11 y/o. Her periods are regular every 28-30 days, heavy bleeding 4-5 days. She is s/p bilateral tubal ligation at 38 y/o where she was told she had mild endometriosis but she was too scared to have it operated on so did not follow up with OBGYN.

- **Social Hx:** She is divorced, has been dating someone new for the past year. She lives in house with her children and works as a patient care assistant.
Case 3: continued

- **Physical exam:**
  - Abdominal: mild tenderness in lower abdomen, no rebound tenderness
  - Pelvic: Multigravida cervix with normal discharge, no vaginal lesions
  - Bimanual exam: anteverted uterus, no adnexal masses
  - Rectovaginal Exam: No nodularity palpated

- **Labs**
  - B-hcg negative
  - CBC and BMP normal
  - UA and Urine culture normal
  - Screen for STD’s is negative
  - Affirm Negative

- **Transvaginal Ultrasound:** Normal endometrial stripe, normal ovaries and uterus, no masses or cysts.