Diagnosis & Management of Endometriosis: Pathophysiology to Practice
Purpose & Content of Module

- Understand the history and pathophysiology of endometriosis
- Understand the critical need for timely diagnosis and effective intervention
- Understand the considerable effects and cost burdens of this chronic disease and employ best-practice techniques to mitigate them
Introduction

- Endometriosis Defined
- Symptomology
- Historical Background
- Pathogenesis
- Epidemiology & Pathophysiology
- Economic Impact
Endometriosis Defined

- An estrogen-dependent disease frequently resulting in substantial morbidity, severe pelvic pain, multiple surgeries, and impaired fertility
- Clinically defined as presence of endometrial-like tissue found outside uterus, resulting in sustained inflammatory reaction
Endometriosis Defined

Characterized by microscopic internal bleeding, development of painful endometriomas, inflammation, fibrotic scarring, and formation of adhesions; distortion of pelvic anatomy may also be present.
Endometriosis Defined

- Ovary (most common)
- Cul-de-sac
- Uterosacral ligaments
- Broad ligament
- Fallopian tubes
- Round ligaments
- Vagina
- Rectosigmoid and bowel
- Urinary bladder and ureters
Endometriosis Defined
Endometriosis Defined

• Leading cause of gynecologic hospitalization and hysterectomy
• Efficacious treatment requires multidisciplinary approach
• Corresponds to high association of co-morbid conditions
• “Disease of theories”; definitive cause or causes remain under debate, though associations with number of hereditary, environmental, epigenetic, and menstrual characteristics exists
Theories of Pathogenesis

- Retrograde menstruation (*Sampson’s Theory*)
  - Endometrial fragments transported through fallopian tubes at time of menstruation and implant at intraabdominal sites

- Müllerian (Coelomic) metaplasia theory (*Meyer’s Theory*)
  - Metaplastic transformation of pelvic peritoneum

- Lymphatic spread (*Halban’s Theory*)
  - Substances released/shed from endometrium induce formation of endometriosis
Theories of Pathogenesis

However, since retrograde menstruation is essentially universal, host factors must impact the development of “disease”, such as:

• variations in the ability to “clean up” menstrual debris, probably reflecting immunologic events.
• Genetic differences in the tendency to develop painful conditions
• Medical and psychological comorbidities
Symptomology

- Ectopic pregnancy, pelvic infection, and ovarian torsion may mimic symptoms.
- Classic signs: severe dysmenorrhea, deep dyspareunia, chronic pelvic pain, Middleschmertz, cyclical or perimenstrual symptoms.
- Typically develops on pelvic structures, i.e., rectovaginal septum, bladder, bowels, intestines, ovaries, and fallopian tubes.
- Less commonly found in distant regions, e.g., diaphragm, lungs (inducing catamenial pneumothorax), and rarely, areas far outside abdominopelvic region.
- Ovaries among most common of locations; gastrointestinal tract, urinary tract, soft tissues, and diaphragm follow.
- May present with varied symptoms including bowel obstruction, melena, hematuria, dysuria, dyspnea, and swelling in soft tissues.
- Degree of disease present has no correlation with severity of pain or symptomatic impairment.
Clinical Presentation

Symptoms vary but typically reflect area of involvement and may include:

- Dysmenorrhea
- Heavy or irregular bleeding
- Cyclical/noncyclical pelvic pain
- Lower abdominal or back pain
- Dyschezia, often with cycles of diarrhea/constipation
- Bloating, nausea, and vomiting
- Inguinal pain
- Dysuria
- Dyspareunia with or without penetration
- Nodules may be felt upon pelvic exam
- Imaging may indicate pelvic mass/endometriomas
Historical Background

- Characteristics of disease described at least as far back as 1600 BCE
- Schrön described a “female disorder in which ulcers appear[ed] in the abdominal, the bladder, intestines and outside the uterus and cervix, causing adhesions”
- First histological description credited to Von Rokitansky
- Cullen later suggested endometriomas (“adenomyomas”) resembled mucous membrane of uterus
- Sampson generally credited for providing first theory on pathogenesis; coined term “endometriosis” in 1921
Pathogenesis

- No single theory sufficiently explains pathogenesis.
- Genetics, biomolecular aberrations in eutopic endometrium, dysfunctional immune response, anatomical distortions, and proinflammatory peritoneal environment may all ultimately be involved.
- 3 distinct disease entities, each with different pathogenesis: peritoneal, ovarian, deeply fibrotic.
- 5 key processes of development: adhesion, invasion, recruiting, angiogenesis, proliferation.
Pathogenesis

- *In situ* from wolffian or mullerian duct remnants (“metaplastic theory”)
- Coelemic metaplasia
- Sampson’s theory
- Iron-induced oxidative stress
- Stem cells
Epidemiology & Pathophysiology

• 176 million women globally; 775,000 in Canada and 8.5 million in North America
• Infertility among chief clinical findings
• No known prevention
• Specific menstrual characteristics may be associated; decreased risk with late age at menarche and shorter menstrual cycles with longer duration of flow
• Family history cannot be undervalued; near 10-fold increased risk in women with first-degree relatives who have disease endometriosis
Epidemiology & Pathophysiology

• Possible dioxin/environmental pollutant link
• No particular demographic, personality trait, or ethnic predilection
• Inverse BMI relationship
• No definitive association with nutrition, exercise, personality traits, or other lifestyle variables
• Are women with endometriosis more attractive?
Economic Impact

• $119 billion annually in associated costs can be attributed to endometriosis

• Intangible costs cannot be undervalued; 72% report having ≥ 8 endometriosis-related or coexisting symptoms interfering with daily life and work

• Significant loss of productivity exists: 11 hours per woman per week; 38% more than for women with similar symptoms without disease

• Direct endometriosis-related costs considerable; driven by hospitalizations

• Females < 23 years old constitute > 20% of endometriosis-related outpatient visits

• Women with endometriosis incur total medical costs 63% higher than average
Comorbidities

- Adhesions
- Infertility
- Risk of Adverse Pregnancy Outcome & Preterm Birth
- Dyspareunia
- “Evil Triplets” of Pelvic Pain: Interstitial Cystitis, Pudendal/Levator Neuralgia, & Endometriosis
- Cancer & Autoimmune Connection
Adhesions

• “Connections between opposing serosal and/or nonserosal surfaces of the internal organs and the abdominal wall, at sites where there should be no connection”

• Highly common co-morbidity in endometriosis patients, yet remains neglected aspect of treatment

• In addition to anatomic distortions and surgical complications, adhesions may also play role in development of ovarian endometriomas and deeply invasive nodules

• Costly; high incidence of adhesion formation postsurgically underscores critical importance of optimizing surgical techniques to potentially reduce formation

• Barriers, surgical modalities may reduce incidence

• Growing awareness will lead to further development of products, improved surgical techniques, research data, and increased favorable clinical outcome
Infertility

- Up to 50% of those with endometriosis may suffer from infertility
  - Distorted pelvic anatomy/impaired oocyte release or inhibit ovum pickup and transport
  - Altered peritoneal function
  - Endocrine and anovulatory disorders, including LUF
  - Impaired implantation
  - Progesterone resistance
  - Decreased levels of cellular immunity
Clinical focus often on infertility related to the disease, yet it is known that endometriosis may also lead to specific pregnancy complications including spontaneous hemoperitoneum in pregnancy (SHiP), obstetric bleeding, pregnancy-induced hypertension, preeclampsia, and preterm birth.
Dyspareunia

- Characterized as sexual dysfunction manifesting as pain in the reproductive organs before, during, or soon after sexual intercourse
- Though frequently depicted as psychogenic, dyspareunia is actually often the result of organic, multidisciplinary cause
- May affect as many as 80% of endometriosis patients; cardinal symptom along with pelvic pain and dysmenorrhea
- Practitioners should inquire, even in absence of complaint, if dyspareunia is present
- Differential diagnosis includes interstitial cystitis, pelvic congestion syndrome, levator ani muscle myalgia, adenomyosis, leiomyoma, ovarian remnant syndrome, uterine retroflexion, irritable bowel syndrome, and mechanical trauma
- Medical treatment, surgical intervention, and combination therapy may help improve symptoms
- Laparoscopic excision has been demonstrated to significantly improve deep dyspareunia as well as quality of sex life
The “Evil Triplets” of Chronic Pelvic Pain: Interstitial Cystitis, Levator Neuralgia, & Endometriosis

- Interstitial cystitis characterized by urinary urgency, frequency, pelvic pain, and dyspareunia without presence of infection
- Previously dubbed an “evil twin” of chronic pelvic pain along with endometriosis
- Pudendal neuralgia may present as tenderness with trophic changes, including abnormal skin texture and structure, reduced blood flow, tissue ischemia, thickening of subcutaneous tissue, and underlying muscle atrophy
- Physical therapy, pudendal nerve block, and surgical intervention may be warranted
- Increased incidence of pudendal neuralgia (88.5%) in endometriosis and interstitial cystitis patients suggests updated classification to “evil triplets”
Cancer & Autoimmune Connection

- Modifications to standard treatment regimens remain unjustified at this time; however, providers of all disciplines should be aware of increased risk profile and strive for early disease detection.
- Though frequently trivialized, disease may be related to a number of hereditary, environmental, epigenetic, and menstrual characteristics, some sharing certain common processes with specific cancers.
- High association between endometriosis and a number of autoimmune diseases, multiple chemical sensitivities, inflammatory bowel disease, food intolerances, allergies, and chronic fatigue.
- “The histogenesis of endometriosis and endometriosis-associated ovarian cancer is [one of the] most mysterious aspects of pathology.”
- Endometriosis may accelerate development of ovarian cancer by 5.5 years.
- Epidemiological findings on the association between endometriosis and cancer remain elusive.
Diagnosis

• Barriers to Diagnosis
• Clinical Diagnosis: Pelvic Examination & Pain Mapping
• Imaging Studies
• Surgical Diagnosis & Staging
Barriers to Diagnosis

• An often underappreciated diagnosis
• Shareholders suffer a delay in diagnosis, on average, of 7 to 12 years and may present to 5 or more physicians before symptoms are addressed
• May be mistakenly dismissed as routine menstrual pain, particularly in younger women
• Lack of nonsurgical markers contributes significantly to delay in diagnosis and timely intervention
Physical examination has poor sensitivity, specificity, and predictive value in the diagnosis of endometriosis.

Combination of history, physical examination, and laboratory and diagnostic studies is indicated to determine cause of pelvic pain and rule out nonendometriosis concerns.

“Pain mapping” may help isolate location-specific disease such as nodular masses in posterior rectovaginal septum.

Absence of evidence during exam is not evidence of disease absence.
Imaging Studies

• Helpful, but not without drawbacks and limitations
• MRI may detect even smallest of lesions and distinguish hemorrhagic signal of endometriotic implants; superior to CT scan in detecting limits between muscles and abdominal subcutaneous tissues
• MRI demonstrated to accurately detect rectovaginal disease and obliteration in more than 90% of cases when ultrasonographic gel was inserted in the vagina and rectum
• Transvaginal or endorectal ultrasonography may reveal ultrasonographic features varying from simple cysts to complex cysts with internal echoes to solid masses, usually devoid of vascularity
• CT may reveal endometriomas appearing as cystic masses; however, appearances are nonspecific and imaging modalities should not be relied upon on for diagnosis
Surgical Diagnosis & Staging

• Laparoscopic intervention is primary means of definitive diagnosis
• Clinically visualized findings may represent “tip of the iceberg”
• Though glands and stroma represent gold standard diagnosis, fibrosis in combination with hemosiderin-laden macrophages may be sufficient for presumptive diagnosis
• Accuracy of diagnosis depends on ability of surgeon to adequately identify disease
“The American Society for Reproductive Medicine’s current classification of endometriosis in stages 1–4 is the most widely used and accepted staging system; however, it does not correspond well to pain and dyspareunia, and fecundity rates cannot be predicted accurately. As a result, attempts to develop a staging system establishing a common language in surgical findings to enable specificity of diagnosis, standardize comparisons, and facilitate research has been undertaken.” [Adamson & Pasta]
Figure 3. Staging: American Society for Reproductive Medicine Revised Classification of Endometriosis

**STAGE I (MINIMAL)**

- **PERITONEUM**
  - Superficial Endo — 1-3cm: -2
  - L. OVARY
  - Superficial Endo — <1cm: -1
  - Filmy Adhesions — <1/3: -1
  - TOTAL POINTS: 4

**STAGE II (MILD)**

- **PERITONEUM**
  - Deep Endo — >3cm: -6
  - L. OVARY
  - Superficial Endo — <1cm: -1
  - Filmy Adhesions — <1/3: -1
  - TOTAL POINTS: 6

**STAGE III (MODERATE)**

- **PERITONEUM**
  - Deep Endo — >3cm: -6
  - L. OVARY
  - Superficial Endo — <1cm: -1
  - Filmy Adhesions — <1/3: -1
  - TOTAL POINTS: 6

**STAGE III (MODERATE)**

- **PERITONEUM**
  - Superficial Endo — >3cm: -3
  - L. TUBE
  - Dense Adhesions — <1/3: -18
  - L. OVARY
  - Deep Endo — <1cm: -4
  - Dense Adhesions — <1/3: -4
  - TOTAL POINTS: 51

**STAGE IV (SEVERE)**

- **PERITONEUM**
  - Superficial Endo — >3cm: -3
  - L. TUBE
  - Dense Adhesions — >2/3: -16
  - L. OVARY
  - Deep Endo — <1cm: -1
  - Dense Adhesions — >2/3: -16
  - TOTAL POINTS: 114

*Point assignment changed to 10
**Point assignment doubled
Surgical Diagnosis & Staging

**Least Function (LF) Score at Conclusion of Surgery**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Left</th>
<th>Right</th>
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</thead>
<tbody>
<tr>
<td>4</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Mild Dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Moderate Dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Severe Dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Absent or Nonfunctional</td>
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<td></td>
</tr>
</tbody>
</table>

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

**Endometriosis Fertility Index (EFI)**

### Historical Factors

<table>
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<th>Factor</th>
<th>Description</th>
<th>Points</th>
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<tbody>
<tr>
<td>Age</td>
<td>If age is &lt; 35 years</td>
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</tr>
<tr>
<td></td>
<td>If age is 36 to 38 years</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>If age is ≥ 40 years</td>
<td>0</td>
</tr>
<tr>
<td>Years Infertile</td>
<td>If years infertile is ≤ 3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>If years infertile is &gt; 3</td>
<td>0</td>
</tr>
<tr>
<td>Prior Pregnancy</td>
<td>If there is a history of a prior pregnancy</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>If there is no history of prior pregnancy</td>
<td>0</td>
</tr>
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</table>

**Surgical Factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>LF Score</td>
<td>If LF Score = 7 to 8 (high score)</td>
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</tr>
<tr>
<td></td>
<td>If LF Score = 4 to 6 (moderate score)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>If LF Score = 1 to 3 (low score)</td>
<td>0</td>
</tr>
<tr>
<td>AFS Endometriosis Score</td>
<td>If AFS Endometriosis Lesion Score is &lt; 16</td>
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</tr>
<tr>
<td></td>
<td>If AFS Endometriosis Lesion Score is ≥ 16</td>
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</tr>
<tr>
<td>AFS Total Score</td>
<td>If AFS total score is &lt; 71</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>If AFS total score is ≥ 71</td>
<td>0</td>
</tr>
</tbody>
</table>

**EFI Score**

\[
\text{EFI} = \text{Total Historical Factors} + \text{Total Surgical Factors}
\]

**Estimated Percent Pregnant by EFI Score**

Treatments

Surgical Intervention
• Laparoscopy
• Hysterectomy/Oophorectomy/Salpingo-oophorectomy

Nonsurgical Therapies
• Medical Therapies
• Alternative Therapies
Surgical Intervention

• Indications for surgical management of endometriosis include:
  – diagnosis of unresolved pelvic pain
  – severe, incapacitating pain with significant functional impairment and reduced quality of life
  – advanced disease with anatomic impairment (distortion of pelvic organs, endometriomas, bowel or bladder dysfunction)
  – failure of expectant/medical management
  – endometriosis-related emergencies, ie, rupture or torsion of endometrioma, bowel obstruction, or obstructive uropathy

• Goals of conservative surgery include removal of disease, lysis of adhesions, symptom reduction and relief, reduced risk of recurrence, and restoration of organs to normal anatomic and physiologic condition

• Complex, deeply infiltrating endometriosis may best be served by tertiary referral center
Laparoscopy

- Surgery to debulk and excise endometriosis may be “more difficult than for cancer”
- Surgical destruction recommended with objective to remove lesions, lyse adhesions, preserve uterus and ovarian tissue, restore normal anatomy
- Incomplete treatment results in persistent symptoms, recurrent disease
- Hysterectomy not a cure; remove disease, not organs
- Indigo carmine or methylene blue may improve detection
- Laparoscopic excision significantly improves fertility, general health, and psycho-emotional status
Appearance of endometriosis with back raised lesions of active endometriosis at the time of laparascopy

Note: Lesions may be raised or flat with red, black or brown coloration; fibrotic scarred areas that are yellow or white in hue; or vesicle that are pink, clear, or red.
Multiple endometrial cysts
“chocolate cysts”
of the ovary
• Probability of pain after hysterectomy is 15% and risk of pain worsening 3% to 5%
• Bilateral oophorectomy rarely indicated in women < 40 years undergoing hysterectomy for endometriosis
• Free ovaries, ureters, and rectum from posterior vagina to the rectovaginal septum
• Deeply fibrotic nodular disease involving the cul-de-sac requires excision of fibrotic tissue from uterosacral ligaments, posterior cervix, posterior vagina, and rectum
• Remaining disease in anterior rectum and vaginal cuff frequently becomes densely adherent to, or invades, bladder and one or both ureters
Nonsurgical Therapies

• Medical Therapies
  – Gonadotropin-releasing hormone agonists (GnRH), oral contraceptives, Danazol®, aromatase inhibitors, and progestins are mainstays

• Alternative Therapies
Medical Therapies

• Superficial surgical and medical treatments often fail
• Combination surgical and medical intervention may provide maximized outcome
• No evidence that medical treatment improves fertility
• Rationale is to induce amenorrhea and create hypoestrogenic environment, theoretically inhibiting growths and promoting temporary regression
• Side effects may be intolerable for some
• Symptoms recur upon cessation of therapy
• Fertility eliminated during treatments as medical suppression inhibits ovulation
• Selection of medical therapy depends on therapeutic effectiveness, tolerability, drug cost, physician experience, and expected patient compliance
Aromatase Inhibitors

- Endometriotic implants express aromatase and consequently generate estrogen, maintaining own viability
- Aromatase inhibitors inhibit local estrogen production in endometriotic implants themselves as well as in ovary, brain, and adipose tissue
- They significantly reduce endometriosis-associated pain when compared with GnRH agonists alone
Oral Contraceptives

- Generally well tolerated; fewer metabolic and hormonal side effects than similar therapies
- Relieve dysmenorrhea through ovarian suppression and continuous progestin administration
- Often a simple, effective choice to manage endometriosis through avoidance or delay of menses for upwards of 2 years
Progestins

• Inhibit growth of lesions by inducing decidualization followed by atrophy of uterine-type tissue
• Compared to GnRH therapy, both modalities show comparable effectiveness
• Medroxyprogesterone acetate proven for pain suppression in both oral and injectable preparations
• Adverse effects include weight gain, fluid retention, depression, breakthrough bleeding
• Mirena® intrauterine device shown to be effective in reducing pain and may be considered alternative to hysterectomy in adenomyosis patients
Nonsteroidal Anti-inflammatory Drugs

- Proven efficacy for treatment of primary dysmenorrhea
- Acceptable side effects
- Reasonable cost
- Ready availability
Danazol®

• Among oldest of medical therapies for endometriosis
• Inhibits midcycle FSH and LH surges and prevents steroidogenesis in corpus luteum
• Higher incidence of adverse effects v more recent therapies
• Androgenic manifestations (oily skin, acne, weight gain, deepening of voice, hirsutism) may be intolerable
Gonadotropin-Releasing Hormone Agonists

- Produces hypogonadotrophic-hypogonadic state through downregulation of pituitary gland
- GnRH agonists as effective as other medical therapies in relieving pain and reducing progression
- Efficacy limited to pain suppression; no fertility improvement
- Disadvantages include high cost of medication, bone mineral density loss, and intolerable hypoestrogenic side effects
- Preoperative therapy reported to reduce pelvic vascularity and size of lesions, thus reducing intraoperative blood loss
- Postoperative therapy may extend surgical relief rates
Alternative Therapies

• Anecdotal experience, preliminary data suggest herbal medicine, physical therapy, diet and nutrition, acupuncture, hypnotherapy, specific supplements, Traditional Chinese Medicine, and other complementary approaches may result in reduction of pain

• Increasing studies may lead to development of additional agents including growth factor inhibitors, angiogenesis inhibitors, cyclo-oxygenase-2 inhibitors, phytochemical compounds, immunomodulators, dopamine agonists, peroxisome proliferator-activated receptor agonists, and more
Conclusion

• Endometriosis is a chronic, costly disease requiring long-term, multidisciplinary treatment

• Profound personal and economic impact underscores urgent need for continued research and improvement in diagnostic and treatment modalities

• Timely intervention and appropriate, multifactorial treatments may restore quality of life, preserve or improve fertility, and lead to long-term effective management in absence of permanent cure