Endometriosis & Cancer Association

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Disclosures

• None
Learning objectives

• Identify the epidemiology and classification of endometriosis

• State the impact of atypical endometriosis on malignant gynecologic tumors

• Discuss potential ways to prevent future ovarian cancer in women with endometriosis
Learning objectives

• Identify the epidemiology and classification of endometriosis

• State the impact of atypical endometriosis on malignant gynecologic tumours

• Discuss potential ways to prevent future ovarian cancer in women with endometriosis
Endometriosis

• 1 in 10 reproductive-aged women (~1 million in Canada)

• ~$2 billion and ~$50 billion in annual costs in Canada and the United States

Levy et al. JOGC 2011;33:830-7
Endometriosis

• Definition:
  – Uterine endometrial tissue, present ectopically elsewhere in the pelvis (or elsewhere)

• Etiology
  – Retrograde menstruation/Immune
  – Metaplasia
  – Blood/lymphatic dissemination

Levy et al.  JOGC 2011;33:830-7
Endometriosis

• Pathophysiology
  – Lesions
    • Estrogen-dependent (systemic and local)
    • Inflammation (prostaglandins)
    • Genetics (inherited and somatic)
  – Uterus
    • Similar changes as in ectopic lesions
  – Comorbidities
    • Myofascial, Urologic, Gastrointestinal
    • Central sensitization

Levy et al. JOGC 2011;33:830-7
Symptoms

• Pelvic pain
  – Menstrual cramps
  – Painful intercourse (deep)
  – Painful bowel movements
  – Cyclical or chronic pelvic pain
• Infertility
• Asymptomatic
Classification

• Anatomic subtype:
  – Superficial
  – Ovarian
  – Deep

• Stage
  – I/II: minimal-mild
  – III/IV: moderate-severe
Superficial endometriosis

• Superficially attached to peritoneum
• Classically pigmented
• Can have other appearances
  – Red
  – White
  – Increased vascularity
Ovarian endometriomas

- Chocolate cysts

- Virtually pathognomonic at ultrasound and surgery
Deep endometriosis

- Invasive > 5mm
- Forms “nodules”
- Can “obliterate” the pouch of Douglas
American Society of Reproductive Medicine: Surgical staging of endometriosis

<table>
<thead>
<tr>
<th>ENDOMETRIOSIS</th>
<th>&lt;1 cm</th>
<th>1-3 cm</th>
<th>&gt;3 cm</th>
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</thead>
<tbody>
<tr>
<td>Peritoneum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Deep</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Ovary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Superficial</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Deep</td>
<td>4</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Left Superficial</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Deep</td>
<td>4</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Posterior Cul-de-Sac Obliteration</td>
<td>Partial</td>
<td>Complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Adhesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Filmy</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dense</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Left Filmy</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dense</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Tube</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Filmy</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dense</td>
<td>4(^1)</td>
<td>8(^1)</td>
<td>16</td>
</tr>
<tr>
<td>Left Filmy</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dense</td>
<td>4(^1)</td>
<td>8(^1)</td>
<td>16</td>
</tr>
</tbody>
</table>

\(^1\) If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16. Staging: Stage I (minimal): 1-5; stage II (mild): 6-15; stage III (moderate): 16-40; stage IV (severe): >40. Revised ASRM Classification. Fertil Steril 1997; 67: 819.
American Society of Reproductive Medicine: Surgical staging of endometriosis

Scoring system for Stages:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Scoring Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>minimal</td>
<td>1-5</td>
</tr>
<tr>
<td>Stage II</td>
<td>mild</td>
<td>6-15</td>
</tr>
<tr>
<td>Stage III</td>
<td>moderate</td>
<td>16-40</td>
</tr>
<tr>
<td>Stage IV</td>
<td>severe</td>
<td>&gt;40</td>
</tr>
</tbody>
</table>

Poorly correlated to symptoms (and malignancy?)
Diagnosis

• Can be suspected based on history and exam
  – Symptoms and/or infertility
  – Tenderness on pelvic exam
• Diagnosis made by surgery and pathology; or
  – Nodularity on pelvic examination
  – Routine or specialized ultrasound
  – MRI
• CA-125 can be elevated; but not a diagnostic or screening tool
Treatment

• Hormonal
  – NSAID
  – Estrogen-progestin contraceptive
  – Progestin (dienogest, norethindrone)
  – Progestin IUD (treatment efficacy can be < 5 yrs)
  – GnRH agonists

• Surgical (laparoscopic)
  – Conservative: ablation or excision
  – Definitive: hysterectomy +/- BSO
Learning objectives

• Identify the epidemiology and classification of endometriosis

• **State the impact of atypical endometriosis on malignant gynecologic tumours**

• Discuss potential ways to prevent future ovarian cancer in women with endometriosis
Other clinical implications

- Extra-pelvic endometriosis (e.g. thoracic)
- Pregnancy complications (e.g. placenta related)
- Autoimmune disease (e.g. MS)
- Coronary heart disease
- Cancer
  - Ovarian: higher
  - Endometrial and breast: equivocal
  - Cervical: lower
What’s the risk of ovarian CA?

- Risk estimates for endometriosis and ovarian CA
Ovarian CA subtypes

- Endometriosis is a risk factor for clear cell and endometrioid (and low-grade serous?)

<table>
<thead>
<tr>
<th></th>
<th>Crude OR (95% CI)</th>
<th>p value</th>
<th>Stratified only OR (95% CI)*</th>
<th>p value</th>
<th>Stratified and adjusted OR (95% CI)†</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive</td>
<td>1.49 (1.34-1.65)</td>
<td>&lt;0.0001</td>
<td>1.53 (1.37-1.70)</td>
<td>&lt;0.0001</td>
<td>1.46 (1.31-1.63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clear-cell</td>
<td>3.73 (3.04-4.58)</td>
<td>&lt;0.0001</td>
<td>3.44 (2.78-4.27)</td>
<td>&lt;0.0001</td>
<td>3.05 (2.43-3.84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>2.32 (1.94-2.78)</td>
<td>&lt;0.0001</td>
<td>2.20 (1.82-2.66)</td>
<td>&lt;0.0001</td>
<td>2.04 (1.67-2.48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1.09 (0.76-1.58)</td>
<td>0.63</td>
<td>1.04 (0.71-1.51)</td>
<td>0.86</td>
<td>1.02 (0.69-1.50)</td>
<td>0.93</td>
</tr>
<tr>
<td>High-grade</td>
<td>1.11 (0.96-1.29)</td>
<td>0.16</td>
<td>1.16 (1.00-1.35)</td>
<td>0.056</td>
<td>1.13 (0.97-1.32)</td>
<td>0.13</td>
</tr>
<tr>
<td>Low-grade</td>
<td>2.02 (1.38-2.97)</td>
<td>&lt;0.0001</td>
<td>2.22 (1.48-3.31)</td>
<td>&lt;0.0001</td>
<td>2.11 (1.39-3.20)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Borderline</td>
<td>1.26 (1.05-1.50)</td>
<td>0.012</td>
<td>1.19 (0.99-1.43)</td>
<td>0.062</td>
<td>1.12 (0.93-1.35)</td>
<td>0.24</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1.27 (0.97-1.67)</td>
<td>0.078</td>
<td>1.19 (0.90-1.57)</td>
<td>0.23</td>
<td>1.12 (0.84-1.48)</td>
<td>0.45</td>
</tr>
<tr>
<td>Serous</td>
<td>1.31 (1.05-1.63)</td>
<td>0.015</td>
<td>1.28 (1.02-1.61)</td>
<td>0.034</td>
<td>1.20 (0.95-1.52)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

OR=odds ratio. *Stratified by age (5 year categories), ethnic origin (non-Hispanic white, Hispanic white, black, Asian, and other). †Stratified by age (5 year categories), ethnic origin (non-Hispanic white, Hispanic white, black, Asian, and other), and adjusted for duration of oral contraceptive use (never, <2 years, 2-4.99 years, 5-9.99 years, ≥10 years), and parity (0, 1, 2, 3, ≥4 children).

Table 3: Association between history of endometriosis and the histological subtypes of ovarian cancer

Atypical endometriosis

• Observation of histologically atypical endometriosis contiguous with ovarian CA
  – Crowding of cells
  – Increase of nuclear/cytoplasmic ratio

• NOTE: Other meanings of “atypical” endometriosis
  – “Atypical” ovarian endometriomas on ultrasound
  – “Atypical” appearance at laparoscopy

Anglesio and Yong, Clin Obstet Gynecol, in press
Atypical endometriosis

• Genomic evidence that atypical endometriosis is the *precursor* to endometrioid/clear cell ovarian CA:
  – Shared regions of loss-of-heterozygosity
  – Shared *ARID1A* mutations (Weigand et al., NEJM)
  – Shared up to 98% of somatic mutations (Anglesio et al., J Path)

• Suggests that endometriosis can accumulate somatic mutations and become atypical, and eventually transform to ovarian CA

Anglesio and Yong, Clin Obstet Gynecol, in press
However...

- Deep endometriosis can also harbour somatic mutations (Anglesio et al., NEJM)

- But extremely rare for deep endometriosis to become atypical and undergo malignant transformation

- Thus, there must be role of ovarian micro-environment

Anglesio and Yong, Clin Obstet Gynecol, in press
Learning objectives

• Identify the epidemiology and classification of endometriosis

• State the impact of atypical endometriosis on malignant gynecologic tumours

• Discuss potential ways to prevent future ovarian cancer in women with endometriosis
What’s the risk of ovarian CA?

• Endometriosis: approx 2 fold increase in risk
  – May be higher with tissue confirmed ovarian endometriosis compared to self-reported history

• However, this is average risk and likely to be heterogeneous – e.g. estrogen exposure

• Goal: Identifying the endometriosis patient who is at higher risk for ovarian CA.
Crux of the problem

- **Endometriosis** *Common*
  - Time?

- **Atypical endometriosis** *Uncommon*
  - Time?

- **Clear cell or endometrioid ovarian CA**
Gyne oncologist

• **What the gyne oncologist is likely to see**
  – Concurrent endometriosis found in 30-40% of clear cell ovarian cancer
  – Atypical endometriosis can be seen in this context
  – Sometimes a continuum is seen consisting of endometriosis, atypical endometriosis, and frank carcinoma
General gynecologist or family physician

• What we’re more likely to see
  – Patient with benign ovarian endometrioma
    1) What’s the risk of ovarian CA?
    2) How can we prevent and who’s at higher risk?

  – Atypical endometriosis found on pathology, in what looked like a benign endometrioma
    1) How frequent is this finding?
    2) How to manage?
General gynecologist or family physician

• What we’re trying to avoid
  – Published case report
  – Age 24: MIS left ovarian cystectomy → endometrioma
  – Age 29: MIS right ovarian cystectomy → endometrioma with atypical endometriosis
  – Age 33: MIS bilateral ovarian cystectomies → right endometrioid ovarian CA
General gynecologist or family physician

• What we’re more likely to see
  – Patient with benign ovarian endometrioma
    1) What’s the risk of ovarian CA?
    2) How can we prevent and who’s at higher risk?
  – Atypical endometriosis found on pathology, in what looked like a benign endometrioma
    1) How frequent is this finding?
    2) How to manage?
How can we prevent ovarian CA?

• Factors that may reduce risk:
  – Hormonal therapy
    • Combined oral contraceptives (dose response)
    • Progestin
    • Progestin IUD
  – Parity (vs. nulliparity or infertility)
  – Tubal ligation (salpingectomy); Hysterectomy
  – Oophorectomy and complete surgical removal of endometriosis
Who’s at higher risk of ovarian CA?

• Examples of women with endometriosis who may be at higher risk for ovarian CA:

<table>
<thead>
<tr>
<th>OCP use</th>
<th>Parity</th>
<th>Tubal ligation</th>
<th>Endometriosis</th>
<th>Family history</th>
<th>Genetic risk quintile</th>
<th>Lifetime risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>5</td>
<td>6.47%</td>
</tr>
<tr>
<td>Never</td>
<td>1 birth</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
<td>7.99%</td>
</tr>
</tbody>
</table>

• **Problem**: we don’t know which of our patients are at genetic risk quintile 4-5
Case 1

• 50 year old perimenopausal G0 with symptomatic left sided 5 cm endometrioma
  – Hypertension, Smoker
  – BMI 40
  – Previous laparotomy, left ovarian cystectomy
  – No previous tubal ligation

• CA-125: 100

• Exam: evidence of Stage IV endometriosis
Case 1

• **Management:**

• Surveillance until menopause?

• Try hormonal therapy, and surveillance?

• Surgery (oophorectomy)?
Case 1

• Surveillance until menopause?
  – Advantages
    • Avoid surgical risk
  – Disadvantages
    • Will endometrioma resolve, and if so, how long will it take?
    • If endometrioma no longer apparent on ultrasound, is it truly resolved or is there still endometriosis in the ovary that could become atypical?
Case 1

• **Hormonal therapy, with surveillance?**
  
  – Advantages
    • Improvement in symptoms and reduce size of cyst
    • Chemoprevention
  
  – Disadvantages
    • Clot risk (if combined estrogen-progestin)
    • If endometrioma no longer apparent on ultrasound, is it truly resolved or is there still endometriosis in the ovary that could become atypical?
Case 1

• Surgery? (oophorectomy, removal of endometriosis, +/- hysterectomy and bilateral salpingectomy)
  – Advantages
    • Tissue diagnosis
    • Prevention of future ovarian CA?
  – Disadvantages
    • Surgical risk (Stage IV endometriosis)
Case 1

- Patient opts for surgery: hysterectomy, BSO, complete removal of endometriosis

- 6 week post-op visit: Patient presents with significant hot flushes. What type of HRT?
  - Estrogen and Progesterone
General gynecologist or family physician

- What we’re more likely to see
  - Patient with benign ovarian endometrioma
    1) What’s the risk of ovarian CA?
    2) How can we prevent and who’s at higher risk?

  - Atypical endometriosis found on pathology, in what looked like a benign endometrioma
    1) How frequent is this finding?
    2) How to manage?
Atypical endometriosis in (benign) endometrioma

• How frequent?
  – Risk of atypical endometriosis in ovarian endometriosis approx 1-2% (4/255)

• How to manage?
  – No guidelines
  – Possibilities: Surveillance? Hormonal therapy? Repeat surgery?

Histopathology 1997;30:249-55
Case 2

• 30 year old, G0, with infertility
  – History/physical suspicious for endometriosis
  – AMH = 2.0 ng/mL
  – Workup shows 5cm right endometrioma
  – Patient opts for laparoscopy, cystectomy done

• **Pathology**: right endometrioma with evidence of atypical endometriosis, no malignancy

• Post-operative U/S: 1cm “follicle” in right ovary
Case 2

• Management?

• Expectant and try for pregnancy, re-evaluate postpartum?

• Hormonal therapy and proceed to ART, then re-evaluate postpartum?

• Oophorectomy, then try for pregnancy?
Case 2

• Expectant and try for pregnancy, re-evaluate postpartum?
  – Advantages
    • Preserve fertility, spontaneous conception
  – Disadvantages
    • Residual atypical endometriosis present?
Case 2

- Hormonal therapy and proceed to ART, then reevaluate post-partum?
  - Advantages
    - Chemoprevention
    - Preserve fertility
  - Disadvantages
    - Residual atypical endometriosis present?
    - ART required (e.g. cost)
Case 2

• Oophorectomy, then try for pregnancy?
  – Advantages
    • Prevention of ovarian CA?
  – Disadvantages
    • Loss of ovary – but AMH reasonable and could conceive from other ovary
Case 2

• Patient opts for oophorectomy, conceives spontaneously from remaining ovary

• 6 week post-partum visit: Patient asks about spacing next pregnancy. What type of family planning?
  – Hormonal (estrogen-progestin or progestin)
Take home points

• Identify the epidemiology and classification of endometriosis

Endometriosis is common, and the ovarian subtype appears to be at risk for malignant transformation
Take home points

• State the impact of atypical endometriosis on malignant gynecologic tumors

Genomic evidence that endometriosis can become atypical, which is a precursor to ovarian CA (clear cell or endometrioid)
Take home points

• Discuss potential ways to prevent future ovarian cancer in women with endometriosis

Possibilities: Hormonal therapy, Parity, Tubal ligation (Salpingectomy), Hysterectomy, Oophorectomy, Complete surgical removal of endometriosis
Questions?

Email:

Paul.Yong@vch.ca or PYong@cw.bc.ca

BC Women’s Centre for Pelvic Pain and Endometriosis:

Http://www.womenspelvicpainendo.com