Introduction to Gynecologic Oncology

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Objectives

Endometrial Neoplasia

- Endometrial hyperplasia and cancer:
  - Discuss the epidemiology and risk factors for endometrial neoplasia.
  - Discuss the clinical presentation and investigation of women presenting with symptoms of endometrial neoplasia.
  - Discuss the different pathologies and prognostic factors in endometrial neoplasia.
  - Discuss the principles and options for treatment of women with endometrial neoplasia.

Objectives

Pelvic Mass and Ovarian Cancer

- Discuss the differential diagnosis for a woman presenting with a pelvic mass.
- Discuss the diagnostic work up of a woman presenting with a pelvic mass.
- Discuss risk factors and possible prevention strategies for ovarian cancer.
- Discuss the classification of ovarian cancers based on a woman’s age, and the prognosis for different ovarian tumors.
- Discuss the signs and symptoms of ovarian cancer.
- Discuss the therapeutic management of women with pelvic masses and ovarian cancer, including surgery and adjuvant therapy.

Objectives

Endometrial Neoplasia

Case Discussion

- A 61 years old woman presents with postmenopausal bleeding.
  - What is your differential diagnosis?
  - What history will you elicit?
  - What physical examination will you perform?
  - What investigations will you order?
  - What treatment options would be available based on the diagnosis?

Postmenopausal bleeding

- Atrophy (50%)
- Hyperplasia (15%)
- Polyps (15%)
- Endometrial cancer (10%)
- Cervix, vulva (10%)
- Consider non-gynecologic causes (urinary tract, GI)

Endometrial hyperplasia

- Abnormal proliferation of glands → can progress to cancer
  - Characterized by architecture of glands (simple or complex) and cellularity (atypia or no atypia)
**Endometrial hyperplasia**

- Simple hyperplasia - uniform glands
- Complex hyperplasia - branching glands

**Treatment of endometrial hyperplasia**

- Presence of cellular atypia is the more important prognostic factor
- If atypia – higher risk of cancer (30% for complex hyperplasia with atypia) → surgery (HBSO)
- If no atypia – lower risk of cancer (1-3%) → progestins (Provera)

**Endometrial cancer**

- Estrogen-related
  - Exogenous estrogen
    - HRT without progestins
    - SERM (e.g. Tamoxifen)
  - Endogenous estrogen
    - Obesity
    - PCOS (anovulatory → no progestrone)
- Non-estrogen related
  - High risk histology
    - uterine papillary serous carcinoma
    - clear cell carcinoma
    - leiomyosarcoma, carcinosarcoma
- 20% premenopausal, obese, low grade tumour, good prognosis

**Investigations / work-up**

- History and physical
  - R/O other sources of PMB
- Endometrial biopsy / D&C
- Ultrasound – not necessary investigation for PMB
  - Increased double layer thickness (anterior and posterior walls opposed to each other)

**Endometrial cancer**

- Most common gynecologic malignancy
- ~ 3500 cases per year in Canada (1400 in Ontario)
- Majority have Stage I disease
  - Early presentation with abnormal bleeding
  - Overall 5 year survival ~ 70%
Endometrial cancer

• Surgery
  – Total abdominal hysterectomy, bilateral salpingo-oophorectomy (+/- pelvic nodes)

• Radiation
  – as primary therapy (rare)
  – Adjuvant treatment (if high risk tumour factors)
    • To decrease risk of pelvic recurrence

Summary

• The most common cause of PMB is atrophy

• Any postmenopausal bleeding requires a history, physical, and biopsy

Ovarian Cyst Case Discussion

• A 41 years old woman comes to you after an ultrasound shows a 5 cm ovarian cyst
• What is your differential diagnosis?
• What history and physical examination will you obtain?
• What additional information do you want about the ultrasound?
• What investigations would you order?
• What treatment options will you discuss?

Ovarian Cancer Case Discussion

• A 70 years old woman complains of early satiety and abdominal distension
• What is your differential diagnosis?
• What pertinent history will you elicit?
• What focused physical examination will you perform?
• What investigation will you order?
• What treatment options are recommended?
Pelvic mass

- History
  - Onset
  - Symptoms
    - Changes in bowel and bladder function
    - Increase in abdominal girth
    - Early satiety, decreased appetite
    - Dyspnea

- Differential diagnosis
  - Gynecologic
  - Non-gynecologic (urinary tract, GI)

Pelvic mass - differential

- Age at diagnosis
  - Childhood
    - Ovarian germ cell tumours, malignant
  - Reproductive age
    - Ovarian epithelial tumours, benign (endometrioma, serous cystadenoma)
    - Ovarian germ cell tumours (benign cystic teratoma)
  - Postmenopausal
    - Ovarian epithelial tumours, malignant and benign
    - Ovarian sex-cord/stromal tumours (granulosa cell)
    - GI tumours (cancer)

Ovarian tumours

- Epithelial (80%)
- Germ cell (15%)
- Sex cord-stromal (5%)

Germ cell tumours

- Classification
  - Dysgerminoma (most common)
  - Teratoma
    - Immature
    - mature (benign cystic teratoma, dermoid)
      *reproductive age
    - Endodermal sinus tumour (yolk sac tumour)
  - Embryonal
  - Choriocarcinoma

Characteristics of germ cell tumours

- Younger population (usually < 20 years)
- Usually diagnosed at Stage I
- Conservative surgery (fertility sparing)
- Curative with chemotherapy if metastatic

Sex cord-stromal tumours

- Granulosa cell tumour
  - secretes estrogen → endometrial hyperplasia or cancer in 25%
- Sertoli-Leydig cell tumour
  - Secrete androgens → virilization
Epithelial tumours

- Classification
  - Serous (cystadenoma)
  - Mucinous
  - Clear cell
  - Endometrioid (endometrioma)
  - Brenner (transitional cell)
  - undifferentiated

Serous cystadenoma

Serous cystadenoma

Endometrioma

Mature cystic teratoma

How to investigate a pelvic mass

- History and physical*
- Ultrasound
  - Transvaginal is best
  - Features
    - Simple vs. complex
    - Cystic vs. solid
    - Excrescences, papillations
    - septations
    - ascites
- Other investigations
  - GI symptoms, bleeding or pencil-thin stools → barium enema or colonoscopy
Ovarian cancer

• Symptoms
  – General
  – Appetite / N&V
  – Respiratory
  – Abdominal girth
  – Bladder
  – Bowel

Ovarian cancer

• Lifetime risk ~ 1/70 (1.4%)

• Highest mortality rate of all gynecologic malignancies

• Usually presents as advanced stage
  – 70% will have Stage III/IV

Ovarian cancer

• Risk factors
  (“incessant ovulation”)
  – Early menarche
  – Late menopause
  – Nulliparity
  – Family history

• Protective factors
  (inhibit ovulation)
  – Oral contraceptive
  – Pregnancy / multiparity
  – Breastfeeding

Ovarian cancer

• Surgery
  – TAH BSO, omentectomy, debulking

• Chemotherapy (adjuvant, ie. after surgery)
  – Paclitaxel and Carboplatin

• Treatment goal
  – Prolongation of disease-free survival (not cure)
  – Overall 5-year survival 70-80% if Stage I, 10% if Stage III/IV

Ovarian cancer

[Image of ovarian cancer with dimensions 540.0x720.0]
Is there a role for screening?

- Ultrasound
- CA125
  - Coelomic and mullerian epithelium

These do NOT reduce the mortality from ovarian cancer

### Role of screening - ultrasound

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th># undergoing surgery</th>
<th># cancers detected</th>
<th># false positives</th>
<th>Positive predictive value</th>
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</thead>
<tbody>
<tr>
<td>Andolf (1986)</td>
<td>805</td>
<td>39 (4.8%)</td>
<td>3</td>
<td>36</td>
<td>7.7%</td>
</tr>
<tr>
<td>Bourne (1993)</td>
<td>1000</td>
<td>52 (5.2%)</td>
<td>3</td>
<td>49</td>
<td>5.8%</td>
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<tr>
<td>Weiner (1993)</td>
<td>62</td>
<td>12 (19.4%)</td>
<td>3</td>
<td>9</td>
<td>25%</td>
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<tr>
<td>Van Nagell (2000)</td>
<td>3299</td>
<td>NR</td>
<td>6</td>
<td>NR</td>
<td>NR</td>
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</tbody>
</table>

### Screening with CA125

<table>
<thead>
<tr>
<th>CA125 Level</th>
<th>% proceeding to U/S</th>
<th>Detection rate</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 U/mL</td>
<td>100%</td>
<td>100%</td>
<td>12.7%</td>
</tr>
<tr>
<td>10 U/mL</td>
<td>72.1%</td>
<td>86%</td>
<td>14%</td>
</tr>
<tr>
<td>20 U/mL</td>
<td>25.3%</td>
<td>71%</td>
<td>31.3%</td>
</tr>
<tr>
<td>30 U/mL</td>
<td>8.7%</td>
<td>43%</td>
<td>30%</td>
</tr>
<tr>
<td>35 U/mL</td>
<td>5.6%</td>
<td>43%</td>
<td>43%</td>
</tr>
</tbody>
</table>

### Elevated CA125

- Gynecologic
  - Endometriosis, fibroids, hemorrhagic ovarian cysts, menstruation, PID, pregnancy
- GI / hepatic conditions
  - Acute pancreatitis, colitis, hepatitis, cirrhosis, diverticulitis
- Other malignancies
  - Bladder, breast, endometrium, lung, liver, pancreas, NHL
- Miscellaneous
  - Pericarditis, PAN, renal disease, Sjogren’s syndrome, SLE

### Role of screening – CA125 and ultrasound

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<th>N</th>
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<th># cancers detected</th>
<th># false positives</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akulenko (1992)</td>
<td>1003</td>
<td>1.4%</td>
<td>1</td>
<td>13</td>
<td>7.1%</td>
</tr>
<tr>
<td>Karlan (1993)</td>
<td>597</td>
<td>1.7%</td>
<td>1</td>
<td>9</td>
<td>10%</td>
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<tr>
<td>Muto (1993)</td>
<td>384</td>
<td>3.9%</td>
<td>0</td>
<td>15</td>
<td>0</td>
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<tr>
<td>Schwartz (1995)</td>
<td>247</td>
<td>0.4%</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Belinson (1995)</td>
<td>137</td>
<td>1.5%</td>
<td>1</td>
<td>1</td>
<td>50%</td>
</tr>
<tr>
<td>Dorum (1996)</td>
<td>180</td>
<td>7.8%</td>
<td>7</td>
<td>7</td>
<td>50%</td>
</tr>
</tbody>
</table>

### Familial cancer phenotypes

1) Hereditary breast/ovarian cancer syndrome
   - BRCA 1 and 2
   - 3 or more relatives with breast and/or ovarian cancer

2) Hereditary non-polyposis colorectal cancer (HNPCC, Lynch II)
   - “3-2-1” rule (Amsterdam criteria): 3 affected individuals, 2 generations, 1 under age 50
   - Includes colorectal and endometrial cancer most commonly (ovarian cancer – less common)
BRCA1 and BRCA2

- Tumor suppressor genes

- 90% of hereditary ovarian cancer

- Increased lifetime risk of breast and ovarian cancer

<table>
<thead>
<tr>
<th>Population</th>
<th>Lifetime breast cancer risk</th>
<th>Lifetime ovarian cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>11% (1 in 9)</td>
<td>1.4% (1 in 70)</td>
</tr>
<tr>
<td>BRCA1 carrier</td>
<td>50-85%</td>
<td>25-50%</td>
</tr>
<tr>
<td>BRCA2 carrier</td>
<td>50-85%</td>
<td>25%</td>
</tr>
</tbody>
</table>

- Variable frequency in different populations
  - e.g. Ashkenazi Jews, Mediterranean, French Canadian

Features of BRCA mutation carriers

- Earlier age of diagnosis for BRCA1 carriers
  - Mean age ~ 53 years (10 years earlier than sporadic ovarian CA)

- (papillary) serous histology

- Increased risk of fallopian tube cancer

- Low penetrance for endometrial cancer

- Associated malignancies with BRCA2
  - Pancreas, gallbladder, gastric, melanoma, male breast and prostate

Recommendations for BRCA mutation carriers

- Screening at early age for breast cancer
  - Consider age of youngest family member diagnosed with breast cancer

- Prophylactic surgery for ovarian cancer (bilateral salpingo-oophorectomy)
  - Screening with ultrasound and CA125 not helpful in this high risk population
  - Prevents ovarian cancer
  - Reduces risk of breast cancer
  - Recommended ~ age 40 (after completed childbearing)

Summary

- The diagnosis of a pelvic mass depends on the age of the patient and clinical features

- Ovarian cancer has the highest mortality rate of all gynecologic cancers

- There is no effective screening for ovarian cancer