Introduction to Gynecologic Oncology
Department of Obstetrics and Gynecology
University of Western Ontario

Objectives
Cervical Dysplasia and Cancer
- Discuss the incidence and risk factors for cervical dysplasia and cervical cancer.
- Discuss the strategies for prevention of cervical dysplasia and cancer.
- Discuss the investigation and treatment of women with an abnormal pap smear.
- Discuss signs and symptoms and the work up of women with cervical cancer.
- Discuss the staging and treatment options for women with invasive cancer of the cervix.

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.

Cervical Dysplasia Case Discussion
- A 28 year old woman has a Pap test showing a low grade squamous intraepithelial lesion (LGSIL)
- How will you discuss risk factors and prevention?
- How will you discuss investigation?
- How will you discuss treatment options?

Cervical Cancer Case Discussion
- A 47 year old woman presents with post coital bleeding and low back pain
- 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 available?
Cervical cancer in Canada

• 1350 new cases / year of cervical cancer in Canada
• 410 deaths in 1998
• 5 million Pap smears annually
• 8% (~320,000 smears) are abnormal, requiring follow-up
• Potentially preventable disease, but still 11th most common malignancy among women

Pap smear

• Screening tool
• Purpose is to screen for intraepithelial lesions (dysplasia) before they progress to invasive cancer

Screening test

• Natural history of disease understood
• Recognizable latent or early stage
• Acceptable test or examination
• Effective treatment
• Cost effective
• High sensitivity (low false negatives)
• High specificity (low false positives)
• High positive predictive value

Pap smear – screening test

PITFALLS
• False negative Pap smears
  – Sampling errors
  – Errors within laboratory
  – Interpretative errors
• False negative results – 20-30% (sensitivity results of 70-80%)

BENEFITS
• Screening has ↓ incidence and mortality from cervical cancer
• (BC provincial program. Finland, Sweden, and Iceland have nationwide programs)

Strategies to improve Pap smear

• Sample collection
  – Quality of sample collected
    • Inflammatory cells, necrotic debris, blood
  – Instrument to take the sample
    • Need to sample both ectocervix and endocervical canal

Pap smear recommendations

• Start screening as soon as sexually active
  – Possibly applies to lesbians as well
• After 3 normal annual pap smears, then screening q2 years
• Continue screening until age 70
  – Can D/C screening only if 4 normal paps in last 10 years
Reporting of pap smears

Papanicolaou classification
CIN1, 2, 3

Bethesda classification
- Squamous intra-epithelial lesion or neoplasia (SIL)
  - Low-grade (LSIL)
    - CIN1
  - High-grade (HSIL)
    - CIN2 or 3
    - ASCUS (atypical squamous cells of unknown significance)
- Glandular

HPV Vaccination

- Quadrivalent vaccine against HPV 6, 11, 16, 18
- Bivalent vaccine against HPV 16, 18
- Primary prevention indicated in girls and women age 9-26
- Decreases risk of 70% of cervical cancer and 90% of genital condylomas (quadrivalent vaccine)
- Importance of maintaining secondary prevention with Pap test

What to do with an abnormal pap

- HSIL → refer to colposcopy
- LSIL → repeat pap in 6/12
  - If LSIL again → colposcopy
  - If normal → repeat pap in 1 year
- ASCUS
  - If ASC-H (ASCUS, cannot rule out HSIL) → colposcopy
  - Otherwise (if ASCUS only), repeat pap in 6/12
    - If ASCUS again → colposcopy
    - If normal → repeat pap in 1 year

What to do with an abnormal pap

- AGUS (atypical glandular cells of undetermined significance) → refer to colposcopy

Normal pap smear

Pap – LSIL
Pap - HSIL

Dysplasia
- Cervical intraepithelial neoplasia
- Spectrum of pre-invasive squamous disease
  - CIN 1,2,3, LSIL, HSIL
  - Takes many years to develop into cancer
- Risk factors – related to HPV exposure
  - Smoking
  - Multiple partners, high risk male partner
  - Immunocompromised

Colposcopy
- Magnification of cervix (+ vagina, vulva)
- Transformation zone vs. squamo-columnar junction
- Acetic acid
- Schiller’s test (Lugol’s solution)

Normal SCJ

LSIL
Treatment for dysplasia

- Laser
  - Vaporizes tissues
  - Rx - low grade dysplasia, lesions seen in entirety

- Cryosurgery
  - Crystallizes intracellular water
  - Rx - low grade dysplasia, lesions seen in entirety

- Loop excision
  - Wire loop provides histologic specimen (unlike laser and cryosurgery – ablative procedures)
  - Rx - high grade dysplasia (HSIL)

- Cone biopsy
  - Excision of cone or cylinder-shaped portion of cervix
  - Rx - unsatisfactory colposcopy (can’t see entire lesion, or the pap and colposcopic findings are very different), or if you suspect cancer
  - Not the treatment of choice for all other cases of dysplasia (longer, may need general anesthetic, potential pregnancy complications)
Description of findings?

Cervical cancer

• In the presence of a gross lesion on the cervix, a pap smear is NOT appropriate

• Need a biopsy to confirm

Cervical cancer treatment

• Stage I
  – Radical hysterectomy and pelvic lymph node dissection (alternative to surgery – pelvic radiation)
    • Different from simple hysterectomy (need wide margin around cervix)
  – Adjuvant pelvic radiotherapy if nodes (+) or if adverse prognostic factors (deep stromal invasion, lymphovascular space invasion)

• Stage II, III, IV (locally advanced)
  – Pelvic radiotherapy and brachytherapy (internal), with concurrent weekly cisplatin chemotherapy
Summary

- Pap smear is a screening tool for cervical cancer
- Different indications for referral to colposcopy, depending on pap smear result
- Different methods of treating dysplasia, depending on severity
- Any grossly abnormal lesion requires a biopsy (not a pap smear)

Endometrial Neoplasia Case Discussion

- A 61 years old woman presents with post menopausal 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 progesterone)
- Non-estrogen related
  - High risk histology
    - Uterine papillary serous carcinoma
    - Clear cell carcinoma
    - Leiomyosarcoma, carcinosarcoma
- Postmenopausal, Caucasian, slim, high grade tumour, poor prognosis
- 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)

Transvaginal ultrasound

- 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

Endometrial cancer
Endometrial cancer

Summary

• The most common cause of PMB is atrophy

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

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 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 perform?
• What treatment options are recommended?
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
  - Secretes androgens → virilization

Epithelial tumours

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

Serous cystadenoma
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

- 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

Treatment of 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

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></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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<tbody>
<tr>
<td>Andolf (1986)</td>
<td>805</td>
<td>39 (4.8%)</td>
<td>3</td>
<td>36</td>
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<td>Bourne (1993)</td>
<td>1000</td>
<td>52 (5.2%)</td>
<td>3</td>
<td>49</td>
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<tr>
<td>Weiner (1993)</td>
<td>62</td>
<td>12 (19.4%)</td>
<td>3</td>
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<td>Van Nagell (2000)</td>
<td>3299</td>
<td>NR</td>
<td>6</td>
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Screening with CA125

<table>
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<tr>
<th>% proceeding to U/S</th>
<th>Detection rate</th>
<th>PPV</th>
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<tr>
<td>2 U/ml.</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>10 U/ml.</td>
<td>72.1%</td>
<td>86%</td>
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<tr>
<td>20 U/ml.</td>
<td>25.3%</td>
<td>71%</td>
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<tr>
<td>30 U/ml.</td>
<td>8.7%</td>
<td>43%</td>
</tr>
<tr>
<td>35 U/ml.</td>
<td>5.6%</td>
<td>43%</td>
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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

<table>
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<tr>
<th>Study</th>
<th>N</th>
<th>% having surgery</th>
<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>
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<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>
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<td>Belinson (1995)</td>
<td>137</td>
<td>1.5%</td>
<td>1</td>
<td>1</td>
<td>50%</td>
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<td>Dorr (1996)</td>
<td>180</td>
<td>7.8%</td>
<td>7</td>
<td>7</td>
<td>50%</td>
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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>1% (1 in 90)</td>
<td>1.4% (1 in 70)</td>
</tr>
<tr>
<td>BRCA1 carrier</td>
<td>10-45%</td>
<td>25-50%</td>
</tr>
<tr>
<td>BRCA2 carrier</td>
<td>10-85%</td>
<td>20-50%</td>
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</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