Introduction to Gynecologic Oncology

Department of Obstetrics and Gynecology
University of Western Ontario

Western

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 againts 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

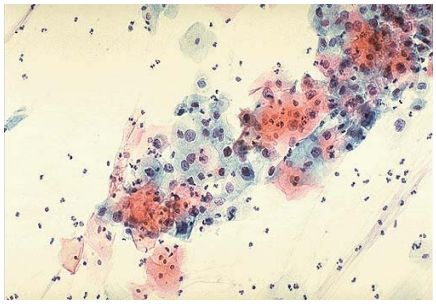
What to do with an abnormal pap

- 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

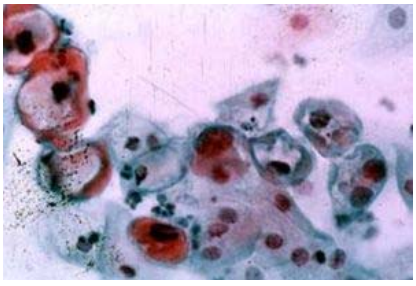
What to do with an abnormal pap

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

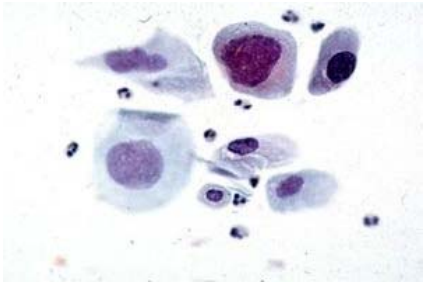
Normal pap smear



Pap – LSIL



Pap - HSIL



Dysplasia

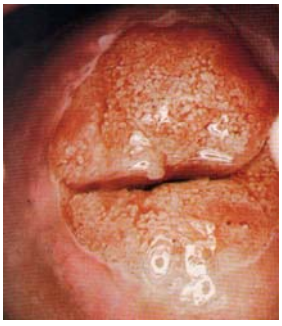
- Cervical intraepithelial neoplasia
- spectrum of pre-invasive squamous disease
  - CIN 1,2,3, LSIL, HSIL
  - takes many years to develop into cancer
- Risk factors – related to HPV exposure
  - Smoking
  - Multiple partners, high risk male partner
  - Immunocompromised

Colposcopy

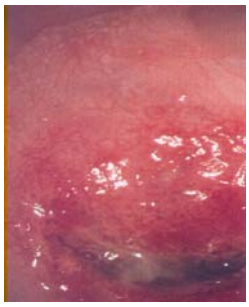
- Magnification of cervix (+ vagina, vulva)
- Transformation zone vs. squamo-columnar junction
- Acetic acid
- Schiller's test (Lugol's solution)

Normal SCJ

Normal SCJ



LSIL



HSIL

HSIL

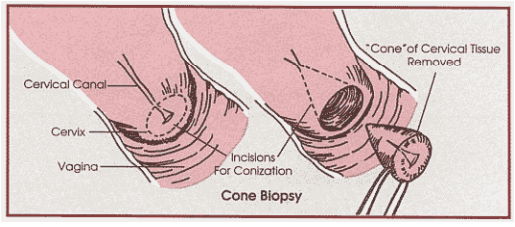
Treatment for dysplasia

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

Treatment for dysplasia

- 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)

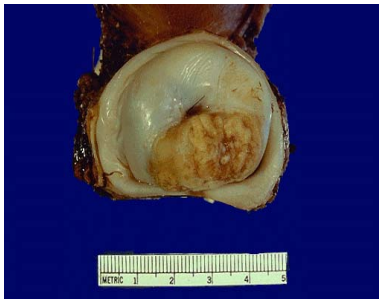
Cone biopsy



Management?

Description of findings?

Cervical cancer



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

- Investigations - clinical staging
  - Pelvirectal exam (assess extent of primary tumour)
  - IVP or U/S (to assess kidneys)
  - CXR
  - CT (not included in FIGO staging)
- Treatment
  - Surgery for early stage (Stage I)
  - Chemoradiation (weekly chemotherapy during pelvic radiation) for locally advanced disease (Stages II, III, IVA)

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)

Cervical cancer treatment

- 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?

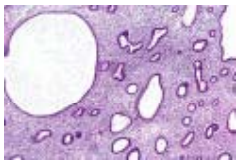
Postmenopausal bleeding

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

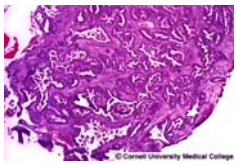
Endometrial hyperplasia

- 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)
- 20% premenopausal, obese, low grade tumour, good prognosis
- Non-estrogen related
  - High risk histology
    - uterine papillary serous carcinoma
    - clear cell carcinoma
    - leiomyosarcoma, carcinosarcoma
- Postmenopausal, Caucasian, slim, high grade tumour, poor 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

Endometrial cancer

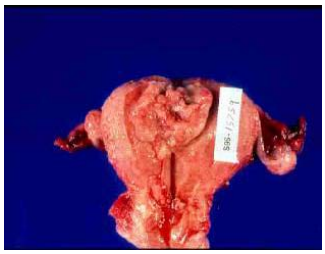
- Most common gynecologic malignancy
- ~ 3500 cases per year in Canada (1400 in Ontario)
- Majority have Stage I disease
  - Early presentation with abnormal bleeding
  - Overall 5 year survival ~ 70%

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

Endometrial cancer

Endometrial cancer



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
  - Secretes androgens → virilization

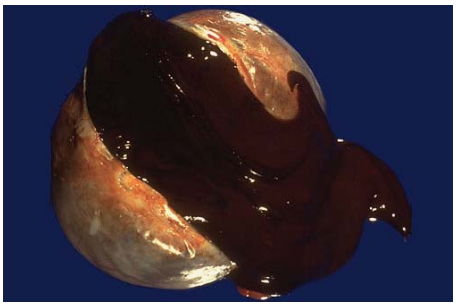
Epithelial tumours

- 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

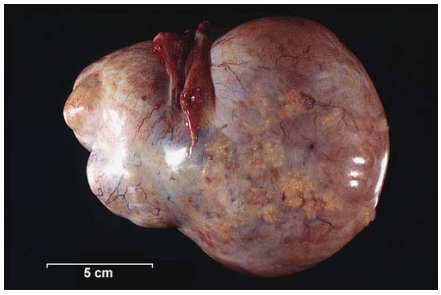
Ovarian cancer

- Risk factors ("incessant ovulation")
  - Early menarche
  - Late menopause
  - Nulliparity
  - Family history
- Protective factors (inhibit ovulation)
  - Oral contraceptive
  - Pregnancy / multiparity
  - breastfeeding

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

Ovarian cancer



Ovarian cancer

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

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

Screening with CA125

	% proceeding to U/S	Detection rate	PPV
2 U/mL	100%	100%	12.7%
10 U/mL	72.1%	86%	14%
20 U/mL	25.3%	71%	31.3%
30 U/mL	8.7%	43%	30%
35 U/mL	5.6%	43%	43%

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

	N	# having surgery	# cancers detected	# false positives	PPV
Akulenko (1992)	1003	1.4%	1	13	7.1%
Karlan (1993)	597	1.7%	1	9	10%
Muto (1993)	384	3.9%	0	15	0
Schwartz (1995)	247	0.4%	0	1	0
Belinson (1995)	137	1.5%	1	1	50%
Dorum (1996)	180	7.8%	7	7	50%

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

Population	Lifetime breast cancer risk	Lifetime ovarian cancer risk
General	11% (1 in 9)	1.4% (1 in 70)
BRCA1 carrier	50-85%	25-50%
BRCA2 carrier	50-85%	25%

- 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