

Gynecologic Oncology

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Endometrial cancer

Endometrial Cancer

- ▶ The most common gynecologic cancer in US.
 - 81.3% survive 5 years
- ▶ Types:
 - Endometrial cancers (97%)
 - Uterine sarcomas (3%)
- ▶ Risk factors:
 - Excess estrogen exposure (postmenopausal therapy, obesity, anovulatory menstrual cycles, tamoxifen), early menarche, nulliparity, late menopause, Lynch syndrome, older age.



Endometrial Cancer

- ▶ Majority (67%) present as clinical stage 1
 - Prognosis dependent on stage
- ▶ Average age of diagnosis – 62
- ▶ Higher incidence in Caucasians.
- ▶ Type 1 (80%)
 - Endometrioid cell type (Grade 1 & 2), estrogen-receptor positive, preceded by intra-epithelial neoplasm
- ▶ Type 2
 - Grade 3 and non-endometrioid histologic cell types (serous, clear cell, carcinosarcoma)



Clinical presentation

- ▶ Abnormal vaginal bleeding – 90%
 1. Post menopausal bleeding
 2. Pre- or perimenopausal with abnormal bleeding
- ▶ Abnormal cervical cytology (pap smear)
 - Adenocarcinoma
 - Atypical glandular cells
 - Endometrial cells
- ▶ Incidental finding on hysterectomy

Work up

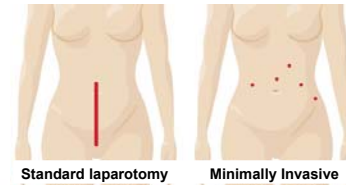
- ▶ Transvaginal ultrasound
- ▶ Endometrial sampling (EMB, D&C)
- ▶ Other imaging: CT, MRI, PET
- ▶ Colonoscopy, Barium Enema for bowel symptoms
- ▶ Serologic marker: CA125 (elevated with metastatic disease)

Treatment

- ▶ Medically fit for surgery:
 - Total hysterectomy and bilateral salpingo-oophorectomy.
 - Exploration of abdominal and pelvic cavity.
 - Surgical staging.
 - Systematic, selective or none
- ▶ Not medically fit for surgery:
 - Tumor directed radiation therapy.
 - Hormonal therapy (progestins, aromatase inhibitors, tamoxifen alternating with megestrol).
 - Chemotherapy.

Surgery

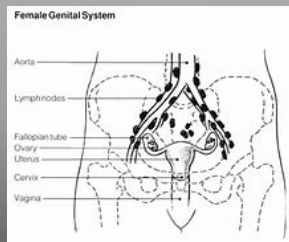
- ▶ Open, robotic-assisted, laparoscopic and vaginal approaches
 - GOG-LAP2



Staging – Lymphadenectomy

- ▶ Selective, systematic or none
- ▶ Risks
- ▶ Therapeutic benefit?

- Patients low risk for nodal metastasis with (Mayo criteria):
 - Tumor less than 2 cm in greatest dimension.
 - Grade 1 or 2.
 - Less than 50% depth of invasion.



Sentinel Lymph Node Mapping

- ▶ Methods
 - Radiocolloid (technecium 99) and Blue Dye
 - Fluorescent medical dyes (Indocyanine Green - ICG)
- ▶ Bilateral cervical injection
- ▶ Video camera sensitive to NIR (700–900 nm)



Treatment

- ▶ Risk stratification
 - Low risk: Grade 1, stage 1A
 - Intermediate risk: Myometrial invasion or occult cervical invasion (stage 2)
 - Stratify into low- or high- intermed. Risk
 - Dependent on age, +LVSI, DOI, grade
 - High risk: Grade 3, stage III

Treatment

- ▶ High intermediate risk
 - VBT
- ▶ Advanced stages and for high risk types
 - Chemotherapy +/- tumor directed radiation
 - Endocrine therapy
- ▶ Recurrent disease
 - Chemotherapy
 - *Immunotherapy
 - Tumor directed radiation
 - Endocrine therapy
 - Surgery

Fertility Sparing Therapy

- ▶ Hormonal
 - Progestins
 - Oral (continuous) vs. IUD
- ▶ Criteria:
 - Low risk group: grade 1–2, clinical stage IA.
 - Close monitoring with endometrial sampling.
 - No contraindication to hormonal therapy
- ▶ Results:
 - Median time to response: 6 months
 - 50–70% complete response.
 - 35% able to achieve pregnancy.
 - 35% recurrence rate.

Ovarian Preservation

- ▶ Premenopausal women with stage IA or IB, low grade.
- ▶ Ovarian preservation may be safe.
 - Multiple retrospective studies show no difference in recurrence and overall survival.

Lynch syndrome

- ▶ 5% of endometrial cancers due to genetic mutations (mainly Lynch syndrome).
- ▶ Women with Lynch syndrome with higher risk for endometrial cancer (60%) and other Lynch syndrome related cancers
 - gastro-intestinal, ovarian, upper genito-urinary, skin
- ▶ DNA Mismatch Repair Testing

5 year survival

Stage I	81–91%
Stage II	67–77%
Stage III	32–60%
Stage IV	5–20%

Ovarian/Fallopian Tube/Primary Peritoneal Cancer

Ovarian/Fallopian Tube/Primary Peritoneal Cancer

- ▶ Leading cause of death from gynecologic cancer in US.
 - 5th most common cause of cancer mortality in women.
 - Lifetime risk 1.3% (general).
- ▶ Median age at diagnosis is 63.
- ▶ 46.5% survive 5 years
- ▶ More than 70% present with advanced disease.

Ovarian/Fallopian Tube/Primary Peritoneal Cancer

- ▶ 90% epithelial carcinoma
 - Others: germ cells, sex-cord stromal, mixed, metastatic from other sites.
- ▶ Histologic subtype
 - serous (70%), clear cell, mucinous, endometrioid, transitional cell.
- ▶ Origin
 - STIN - TP53 mutation and morphologic atypia

Risk Factors

- ▶ Incessant ovulation
 - Nulliparity, Older age at first birth (> 35 years)
- ▶ Age
- ▶ Postmenopausal hormonal therapy
- ▶ Ovarian stimulation for fertilization (for LMP tumors)
- ▶ Endometriosis
 - Increase in endometrioid and clear cell types
 - Risk of transformation 2.5%
- ▶ Obesity
 - Slight increase risk with BMI > 30 kg/m²
- ▶ Ovarian cancer susceptibility genes
 - BRCA1 (age 50) and BRCA2 (age 60)
 - Lynch syndrome
 - Others: BRIP1, RAD51C, RAD51D, CHEK2.
 - US - 15% pts have BRCA mutation; 3-14% with Lynch
- ▶ Family history of ovarian cancer - 5.5%
 - (although most are now BRCA)

Protective factors

- ▶ Use of oral contraceptive pills
 - RR decrease by 20% for each 5 years of use
 - Protective effect persist 30 years after cessation
- ▶ Multiparity
- ▶ Salpingo-oophorectomy
- ▶ Tubal ligation
 - Some report at least a third in risk reduction
- ▶ Breast feeding
- ▶ Younger age at first pregnancy and birth (≤ 25 years)
- ▶ Hysterectomy

Screening test

- ▶ NO EFFECTIVE SCREENING TEST YET FOR GENERAL POPULATION.
- ▶ Previously studied screening methods
 - CA125 and pelvic ultrasound.
 - UK Collaborative Study, PLCO Cancer Trial.
 - Risk of Ovarian Cancer Algorithm (ROCA).
 - OVA1
 - OvaSure

Clinical Presentation

- ▶ Bloating
- ▶ Increase abdominal girth
- ▶ Difficulty eating, early satiety
- ▶ Abdominal and/or pelvic pain
- ▶ Urinary urgency or frequency
- ▶ Weight loss
- ▶ Shortness of breath
- ▶ Fatigue

- ▶ Adnexal mass
- ▶ Pleural effusion
- ▶ Bowel obstruction

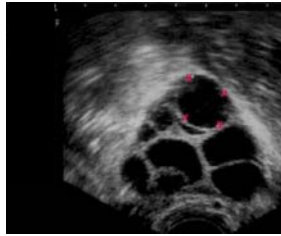


Diagnostic Tests

- ▶ Imaging
 - Ultrasound
 - CT scan
 - MRI
 - PET CT
- ▶ Laboratory evaluation
 - CA125
 - HE4
 - OVA1

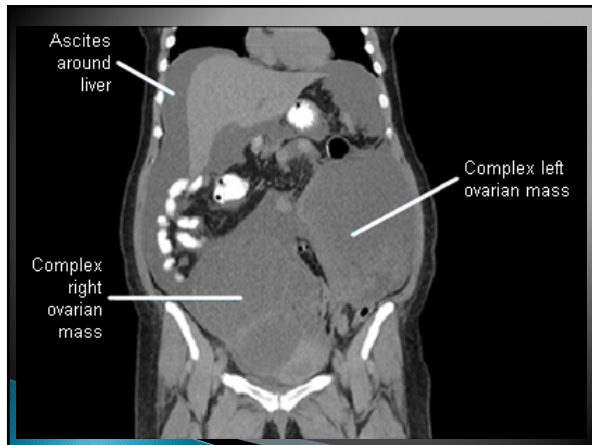
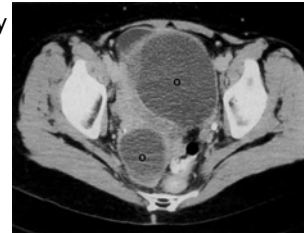
Sonographic findings

- ▶ Solid components
- ▶ Nodularity
- ▶ Papillary features
- ▶ Thick septations
- ▶ Ascites
- ▶ Peritoneal masses
- ▶ Internal blood flow



CT findings suggestive of cancer

- ▶ Pelvic masses
- ▶ Omental caking
- ▶ Lymphadenopathy
- ▶ Ascites
- ▶ Liver lesions
- ▶ Pleural effusions



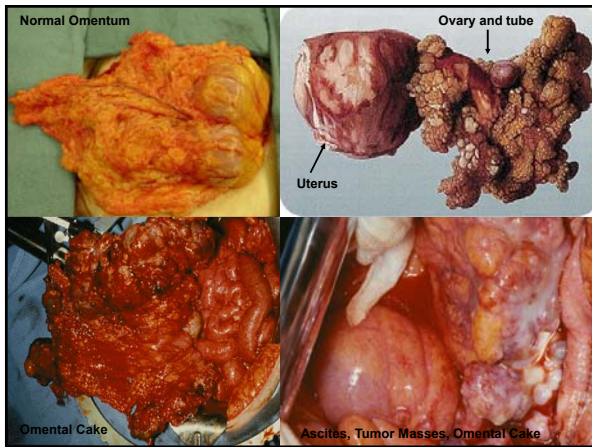
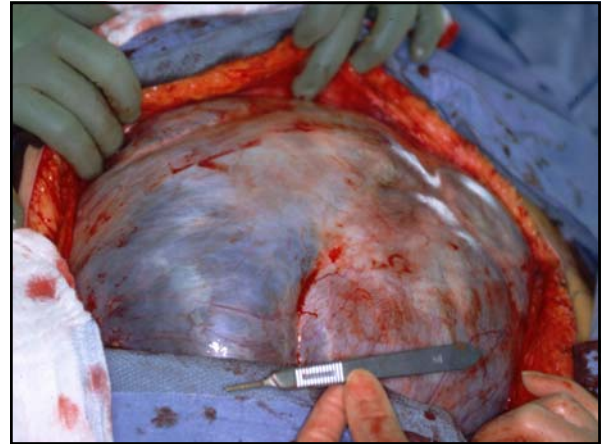
Diagnostic Tests

- ▶ Image-guided biopsy
- ▶ Paracentesis and thoracentesis
- ▶ Rule out extra-ovarian primary
 - Gastrointestinal evaluation
 - Colonoscopy
 - Barium enema
 - Mammography

Treatment

- ▶ **Standard Surgery**
 - Exploratory laparotomy
 - Total abdominal hysterectomy
 - Bilateral salpingo-oophorectomy
 - Omentectomy
 - Lymphadenectomy
 - Appendectomy
 - Biopsies
 - Debulking
- ▶ **Radical debulking may include:**
 - Bowel resections
 - Bladder or ureteral resection
 - Splenectomy
 - Liver resection
 - Peritoneal stripping





Optimal Surgical Cytoreduction

- ▶ Residual disease after cytoreduction inversely correlates with survival.
- ▶ Debulking improves survival with 20 month improved median survival for optimal vs. suboptimal debulked.
- ▶ GOG definition = residual disease < 1 cm in maximal dimension.
- ▶ No visual disease is best.

Adjuvant Chemotherapy

- ▶ Intravenous chemotherapy
- ▶ Intraperitoneal chemotherapy - IV/IP.
- ▶ Hyperthermic intraperitoneal chemotherapy
 - Investigational at this time; although a randomized controlled trial supports the use
- ▶ Clinical Trial Enrollment

Intraperitoneal chemotherapy

- ▶ Intraperitoneal/intravenous chemotherapy
 - Stage III optimally debulked
- ▶ Improved median survival
 - 16 months advantage
- ▶ More side effects (including previous)
 - Catheter complications, infections, abdominal pain, vomiting, metabolic and renal complications

Armstrong et al, 2006, NEJM 354(1):34

Neoadjuvant chemotherapy

- ▶ Candidates:
 - Stage IV disease
 - Stage III
 - Preoperative predictors of unresectable disease
 - Poor surgical candidate
- ▶ 3–4 cycles of IV Chemotherapy.
- ▶ Goals
 - decrease tumor burden/enhance patient's medical status
 - reduce surgical morbidity (ostomy)
 - increase possibility for complete cytoreduction
- ▶ Interval debulking.

Stage, Distribution, and Survival

<u>Stage</u>	<u>Percent</u>	<u>Survival</u>
I	24	95%
II	6	65%
III	55	15-30%
IV	15	0-20%
Overall		50%

American Cancer Society 2000

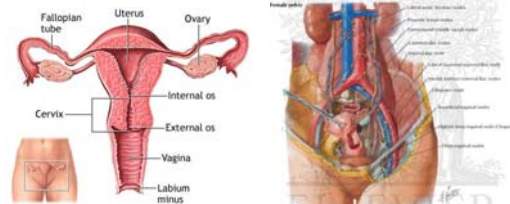
Recurrent Ovarian Cancer

- ▶ Dependent on disease free interval
 - Oligometastatic disease, 6+ months
 - Eligible for secondary debulking
- ▶ Clinical Trial
- ▶ Targeted therapy
 - PARPi, Checkpoint inhibitors
- ▶ Chemotherapy
 - Multiple options for second line regimens.
- ▶ Endocrine therapy.
- ▶ Tumor directed radiation therapy.

Genetic testing

- ▶ Personal h/o of ovarian cancer
- ▶ BRCA and Lynch Syndrome.
- ▶ Why important?
 - May influence treatment recommendations and options.
 - PARP inhibitors
 - Surveillance, healthcare maintenance, prophylactic surgery
 - Information for family members to help them make healthcare decisions for care/prevention.

Cervical cancer



From: Adam.inc

From: netterimages.com

Background

- ▶ Age related disease
- ▶ Mean age of diagnosis in US is 47
 - < 20 yr age – 0/100,000/yr
 - 20–24 yr age – 1.7/100,000/yr
 - Peak at 45–49 yr age – 16.5/100,000/yr
 - < 10% cases in women > 75
- ▶ Histology:
 - 80% are squamous cell.
 - 20% are adenocarcinomas.
 - Rare types: neuroendocrine, glassy cell, etc

Cervical cancer: Risk factors

- ▶ Early onset of sexual activity
- ▶ Multiple sexual partners
- ▶ High risk sexual partners
- ▶ History of sexually transmitted disease
- ▶ Smoking
- ▶ Chronic immunosuppression
- ▶ Certain autoimmune diseases
- ▶ Oral contraceptive use
- ▶ Parity

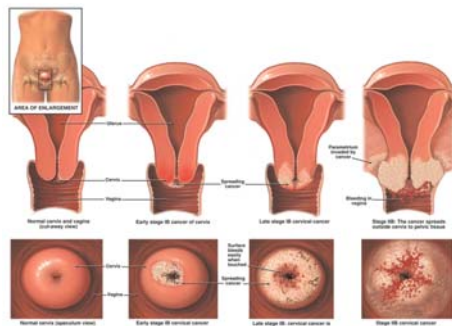
Clinical presentation

- ▶ Symptoms:
 - Early disease is often asymptomatic
 - Abnormal vaginal bleeding
 - Post-coital bleeding
 - Vaginal discharge: watery, mucoid, purulent, malodorous
- ▶ Exam:
 - Visible lesion: exophytic, ulcerative, endophytic
 - 15% have no visible lesions (likely adenocarcinoma)



Diagnosis

- ▶ Pelvic exam
- ▶ Pap smear
- ▶ Colposcopy with biopsies
- ▶ Conization of the cervix
- ▶ Cystoscopy
- ▶ Proctoscopy
- ▶ Imaging – CT, PET CT, MRI
- ▶ Blood work – CBC, LFTs, BMP



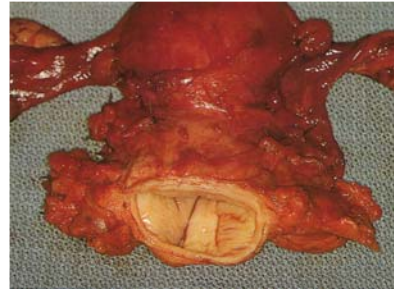
From: womensgovernment.org

Treatment

- ▶ Clinically staged (FIGO) versus TNM
- ▶ Early stage can be treated with surgery or chemoradiation.
 - If surgery:
 - Stage IA1 – simple hysterectomy or conization.
 - Stage IA1 with LVSI – Lymph node dissection/sentinel node.
 - Stage IA2 – IIA – radical hysterectomy with lymph node dissection.
- ▶ Stage IIB–IVA – chemoradiation.
 - May include some bulky stage IB2.
- ▶ Stage IVB – Cisplatin based chemotherapy.
 - Maybe radiation for local control, symptom management.

Surgery

- ▶ Surgical approach
 - Laparotomy – LACCS trial
- ▶ Fertility sparing surgery
 - Radical trachelectomy with lymph node dissection.
- ▶ Lymphadenectomy
 - Full pelvic +/- para-aortic dissection
 - Sentinel lymph node sampling
 - Best in tumors less than 2 cm



Radical Hysterectomy Specimen

recurrent disease

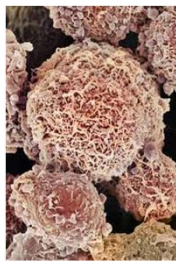
- ▶ Local recurrence
 - Surgery
 - Pelvic exenteration – morbid procedure
 - Chemotherapy
 - Radiation
- ▶ Metastatic
 - Chemotherapy
 - Radiation – if limited disease

5 year survival

- ▶ Stage IA–small IB 80 – 100%
- ▶ Large IB 75 – 90%
- ▶ Stage IIA 71 – 85%
- ▶ Stage IIB 60 – 75%
- ▶ Stage III 30 – 50%
- ▶ Stage IVA 8 – 27%

Human Papilloma Virus

- ▶ Non–enveloped double stranded DNA–virus
- ▶ > 100 types identified
 - 30–40 anogenital types
 - 15 oncogenic types discovered – these can lead to high grade dysplasia and cancer
 - Non–oncogenic types – associated with low grade dysplasia and genital warts.



From: feidaunion.com

Cervical Cancer vaccines

- ▶ Cervarix (GSK)
 - Bivalent vaccine against HPV 16, 18 with cross protection against HPV 31.
- ▶ Gardasil (Merck)
 - Quadrivalent vaccine against HPV 6, 11 (for treatment of genital warts) and HPV 16, 18.
 - Gardasil 9 – 9–valent vaccine against 6,11,16, 18, 31, 33, 45, 52, and 58.

Cervical Cancer Vaccines

- ▶ Clinical trials have demonstrated:
 - Safety with minimal side effects
 - Efficacy
 - Durability
- ▶ Women still need routine pap smears and pelvic exams based on their risk factors.
- ▶ Schedules:
 - Two doses of HPV vaccine are recommended for most persons starting the series before their 15th birthday.
 - Second dose of HPV vaccine 6 to 12 months after the first dose.
 - Adolescents who receive 2 doses less than 5 months apart will require a third dose of HPV vaccine.
 - Three doses of HPV vaccine are recommended for teens and young adults who start the series at ages 15 through 26 years, and for immunocompromised persons.
 - 3-dose schedule is 0, 1-2 and 6 months.
 - Three doses are recommended for immunocompromised persons (including those with HIV infection) aged 9-26 years

Cervical cancer vaccines

- ▶ Routine vaccination starting age 11-12 (may start at age 9)
- ▶ ACIP also recommends:
 - females aged 13 through 26 years
 - males aged 13 through 21 years not adequately vaccinated previously.
- ▶ Gay, bisexual, and other men who have sex with men, transgender people, and for immunocompromised persons (including those with HIV infection) not adequately vaccinated previously
 - Vaccinate through the age 26.

CDC.GOV 2018

Vulvar Carcinoma

Vulvar Cancer

- ▶ 4% of malignancies in female genital tract
- ▶ Average age 65 years but bimodal distribution
- ▶ Two etiologies:
 - Mucosal HPV infection
 - Chronic inflammatory or autoimmune process
 - Lichen sclerosus
- ▶ > 90% are squamous cell histology

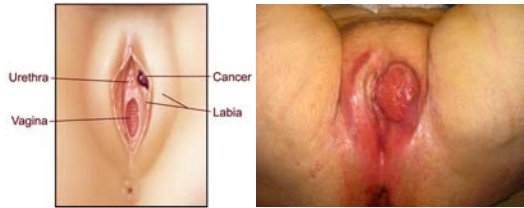
Risk factors

- ▶ Cigarette smoking
- ▶ Vulvar dystrophy (eg. Lichen sclerosus)
- ▶ Vulvar or cervical intraepithelial neoplasia
- ▶ HPV infection
- ▶ Immunodeficiency syndromes
- ▶ Prior history of cervical cancer
- ▶ Northern European ancestry

Clinical presentation

- ▶ Vulvar plaque, ulcer, or mass
- ▶ Pruritis (itching)
- ▶ Pain
- ▶ Vulvar bleeding or discharge
- ▶ Dysuria
- ▶ Enlarge lymph nodes in the groin
- ▶ Asymptomatic

Clinical presentation

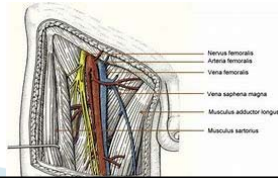


Evaluation

- ▶ Biopsy
 - Confirm diagnosis
- ▶ Rule out metastatic disease
 - PET/CT
 - MRI
- ▶ Cystoscopy
- ▶ Proctoscopy

Treatment

- ▶ Surgically staged
- ▶ Radical wide excision
- ▶ Groin lymph node dissection
 - Vulvar lesion with > 1mm depth of invasion
- ▶ Unilateral versus bilateral groin dissection
- ▶ Sentinel lymph node dissection



Treatment

- ▶ Advanced disease little chance of cure with surgery alone.
- ▶ Neoadjuvant chemotherapy and radiation.
 - Cisplatin day 1, 5 FU infusional day 1-4, repeat 3 weeks later.
 - Concurrent daily radiation.
 - Similar regimens for rectal/anal cancer.
- ▶ Followed by surgery with radical vulvectomy and inguinal lymph node dissection.
 - Adjuvant treatment allows for less morbid surgery.

Treatment

- ▶ Adjuvant radiation
 - Positive/close margins (< 8mm - fixed specimen)
 - Large tumors > 4.1 cm
 - Lymphovascular space invasion
 - 2 or more positive microscopic lymph nodes
 - 1 or more positive macroscopic lymph nodes
- ▶ Recurrent disease
 - Surgery, chemotherapy, radiation

5 year survival

- ▶ Stage I 78%
- ▶ Stage II 58%
- ▶ Stage III 43%
- ▶ Stage IV 13%

Gestational Trophoblastic Disease

Gestational Trophoblastic Disease

- ▶ Proliferative disorder from placental tissue.
 - Heterogenous group of lesions
 - Trophoblastic epithelium of the placenta
- ▶ Described by Hippocrates 400 BC
- ▶ Most curable gynecologic malignancy
 - First cure with chemotherapy 1956 Li et al

Clinical manifestations

- ▶ Vaginal bleeding
- ▶ Enlarged uterus (size > dates)
- ▶ Pelvic pressure, pain
- ▶ Theca lutein cysts
- ▶ Anemia
- ▶ Hyperemesis gravidarum
- ▶ Hyperthyroidism
- ▶ Pre-eclampsia before 20 weeks gestations
- ▶ Passage of hydropic vesicles

Types

- ▶ Hydatidiform Mole
 - Partial or complete
- ▶ Invasive mole
- ▶ Choriocarcinoma
- ▶ Placental Site Trophoblastic Tumor
 - Epithelioid Trophoblastic Tumor

Complete mole

- ▶ Aberrant fertilization resulting in only paternal DNA (46 XX or 46 XY) by:
 - Fertilization of an empty ovum by 2 sperm
 - Fertilization of an empty ovum by single sperm that duplicates
- ▶ Lacks fetus
- ▶ Large uterine size (size > dates)
- ▶ Hydropic, edematous chorionic villi

Complete mole



From: Pregnan-cy.com



From: lookfordiagnosis.com

Partial mole

- ▶ Aberrant fertilization resulting in triploid DNA (69 XXX, 69 XXY, or 69 XYY)
 - Fertilization of ovum by 2 sperms
 - Fertilization of ovum by 1 sperm that duplicates
- ▶ Fetus/embryo present
- ▶ High rate of intrauterine death

Malignant GTN

- ▶ May follow any type of pregnancy
 - After molar pregnancy
 - Persistent disease after uterine evacuation
 - Rates: complete 15–20%, partial 3–5%
 - Follow HCG levels
 - Can be focal or metastatic
 - Most are due to invasive moles, but few choriocarcinoma
 - After regular pregnancy
 - Found by histology or noted rise/persistent of β -HCG
 - Almost always choriocarcinoma

GTN – choriocarcinoma

- ▶ Can arise from any type of pregnancy
- ▶ From cytotrophoblasts
- ▶ Aggressive
- ▶ Early vascular invasion and widespread metastasis
- ▶ Symptoms: irregular vaginal bleeding
- ▶ Exam: large uterus, ovarian cysts, vaginal metastasis (very vascular – never biopsy)

GTN – placental site trophoblastic tumor

- ▶ Can arise from any type of pregnancy
- ▶ From intermediate trophoblasts
- ▶ Rare < 0.2% of all GTNs
- ▶ Slow growing
- ▶ Diagnosed month – years after a term pregnancy.
- ▶ Tumor marker human placental lactogen (hPL)

Diagnosis and treatment

- ▶ Hydatidiform moles (benign)
 - β -HCG, ultrasound
 - Suction curettage
- ▶ Malignant GTN
 - β -HCG, Imaging (ultrasound, CT, MRI)
 - Chemotherapy first line treatment, high cure rate
 - Surgery in refractory focal disease, consider for choriocarcinoma if done with child-bearing, and for PSTT/ETT.

Staging and treatment

- ▶ Based on extent of disease involvement
 - Confined to uterus, local versus distant metastasis.
- ▶ Prognostic score
 - Based on factors such as size of lesion, β -hCG level, number and sites of metastasis, type and time from antecedent pregnancy, prior chemotherapy
 - Influences recommended treatment regimen
- ▶ Treatment with chemotherapy
 - Single agent versus combination therapy

Resources

- ▶ Education
 - Patients, primary care, specialists.
- ▶ Supportive resources
 - Social work, financial services, dietician, genetics counseling, STAR rehab program.
- ▶ Support groups/survivorship programs
- ▶ Palliative care
- ▶ Hospice

Thank you!