Gestational Trophoblastic Disease

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INTRODUCTION

- GTD describes a continuum of lesions that arise from abnormal proliferation of placental trophoblasts.
- Unique, because maternal lesion arises from fetal tissue.
- Ranges from benign hydatidiform mole to invasive mole, malignant choriocarcinoma (CCA), placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT).

- **GTD** = *benign*, non-neoplastic lesions; hydatidiform moles (both partial and complete).
- **GTN** = *invasive disease* (invasive mole, CCA, PSTT, ETT).
EPIDEMIOLOGY

- Estimated incidence of 0.6-1.0 / 1000 pregnancies; 2-3 fold higher (~2 / 1000) in Southeast Asia and Japan

- Two strongest risk factors for complete mole: (1) **Age**, and (2) **prior molar pregnancy**
  - Both very young women and women > 40 have increased risk (>40 is 5-10 fold higher)
  - Risk of second mole is ~ 1%; a third is ~ 15-20%
EPIDEMIOLOGY

- Some weak evidence that vitamin A deficiency is associated with increased rates of molar pregnancy (only complete, not partial moles)

- Locally invasive GTN develops in ~ 15% after molar evacuation

- CCA is ~ 1:50,000 pregnancies; most likely following complete molar pregnancy
PATHOLOGY AND CHROMOSOMAL FEATURES
TROPHOBLASTIC DIFFERENTIATION

- Molar pregnancies develop from **placental trophoblasts**, which is derived from the outermost layer of the blastocyst.

- Trophoblast is composed of **cytotrophoblasts, syncytiotrophoblasts**, and intermediate trophoblasts.

- **Syncytiotrophoblasts** invade the endometrial stroma and upon implantation and secrete **hCG**.

- **Cytotrophoblasts** fuse with syncytiotrophoblasts to form chorionic villi.

- Invasion of healthy trophoblasts into maternal endometrium is normal, tightly regulated event; when regulatory mechanism are impaired, invasive and vascular tumors arise.
Normal chorionic villi

- Cyto-trophoblastic
- Syncytia-trophoblastic
- Intermediate-trophoblastic

Scale: 100 µm
HYDATIDIFORM MOLE

- Molar pregnancies arise from proliferation of cytotrophoblasts and syncytiotrophoblasts, which produce lesions in the maternal decidua

**Complete moles:**
- Early, uniform enlargement of villi with hyperplastic and atypical trophoblasts
- **90% are 46, XX:** they arise from fertilization of anucleated egg by single sperm (duplicates)
- Contain ONLY paternal chromosomes

**Partial moles:**
- **Triploid (69, XXY):** arise from either dispermic fertilization of normal egg or duplication of chromosomes in a single sperm after fertilization of a normal egg
<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathologic Features</th>
<th>Clinical Features</th>
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</table>
| Complete mole| - Diploid (46,XX and some 46,XY)  
- No fetus or embryo  
- Diffuse swelling of villi  
- Diffuse trophoblastic hyperplasia | - Vaginal bleeding  
- Large for date uterine size  
- Bilateral theca lutein cysts  
- hCG can be >100,000 mIU/mL |
| Partial mole | - Triploid (69,XXY; 69,XYY; 69,XXX)  
- Abnormal fetus or embryo  
- Focal swelling of villi  
- Focal trophoblastic hyperplasia with mild atypia | - Symptoms of incomplete or missed abortion  
- Vaginal bleeding  
- hCG rarely elevated >100,000 mIU/mL |

- **Complete mole** = 15-20% trophoblastic sequelae
- **Partial mole** = <5% trophoblastic sequelae
COMPLETE HYDATIDIFORM MOLE
PARTIAL HYDATIDIFORM MOLE

- Partial hydatidiform mole with chorionic villi of varying size and shape with focal edema and **scalloping**, stromal trophoblastic inclusions, and functioning villous circulation, as well as focal trophoblastic hyperplasia
INVASIVE MOLE

- When a hydatidiform mole has invaded the myometrium through the tissue or veins
MANAGEMENT OF MOLAR PREGNANCY
CLINICAL PRESENTATION

- 80-90% of women with a complete hydatidiform mole present with *vaginal bleeding*, occurring 6-16 weeks gestation.
- Other features: larger uterine size than expected for date, hyperemesis, hyperthyroidism.
- hCG can be > 100,000; no fetal heart tones.
- ~ 15% will have bilateral theca lutein cysts.
**DIAGNOSIS**

- **History and physical:**
  - OB and GYN history
  - History of prior molar pregnancy?
  - If vascular lesion, do NOT biopsy

- **Type and Screen, serum hCG level:**
  - If below the discriminatory zone (< 1500), serial hCG levels should be performed every 48-72 hrs
  - If hCG > 100,000, obtain TSH

- **Pelvic ultrasound:**
hCG: quantitative serum hCG is the most accurate disease-specific marker of GTD

- Placental hCG is a glycoprotein of two subunits, a common α subunit of pituitary hCG, and a placenta-specific β subunit

- In normal pregnancy, hCG is essential for maintaining placental vascular supply; as pregnancy progresses, hCG is secreted by syncytiotrophoblasts, increasing to ~ 60,000 mIU/ml at 10 weeks, and then declining to ranges of ~ 12,000 for the remainder of the pregnancy

- hCG secreted by trophoblast-derived moles and GTN are more heterogenous than in a normal pregnancy; results in fragmentation of the hCG molecule and several forms of hCG are present
  - Hyperglycosylated, nicked, C-terminal truncated β subunit, free β subunit, nicked free β subunit, and free α subunit
FALSE-POSITIVE AND FALSE-NEGATIVE HCG

- Most common test is monoclonal antibody sandwich assay
- Some assays produce false-positive or ‘phantom’ hCG results
  - Due to the nonspecific heterophilic antibodies that mimic hCG and can interfere sandwich assay
  - 3-4% of healthy people
  - This large antibody does NOT pass through the urine; can look at hCG levels in the urine
  - Additionally, serial dilution of the serum sample would not show a decrease in the detected antibody

- LH can also cross-react with hCG assay, leading to falsely elevated hCG in women with elevated FSH; perimenopausal or menopausal women may have low levels of hCG
  - Women can be given OCP to suppress LH, followed by measurement of LH and hCG
**DIAGNOSIS**

*Ultrasound* is the primary means of preoperative diagnosis

- Prior to 1980, complete molar pregnancy was most commonly diagnosed in 2nd trimester (16.5 wks)
  - Vaginal bleeding, hyperthyroidism, preeclampsia
- Globally, now diagnosed more frequently in the 1st trimester (11 wks)
  - Has not changed the risk of post-molar GTN
**DIAGNOSIS**

Diagnosis by pathologic examination of curettage tissue:

- **90% of partial moles** are diagnosed following ‘missed or incomplete AB’
  - Why you should follow hCG levels down
- This can be challenging differentiating between complete mole, partial mole, or hydropic abortus
- **P57kip2 protein** is paternally imprinted and *maternally expressed*
  - The villous cytotrophoblasts in complete moles will stain negative (b/c lack maternal chromosomes)
  - **Partial moles will stain positive**
TREATMENT

**Suction evacuation and curettage** is the preferred treatment for women who wish to preserve their fertility.

**Preoperative evaluation:**

- Vitals, CBC, CMP, type and screen, hCG, CXR (some say only with pulmonary symptoms)
- *Rh negative patients should receive RhoGAM because Rh D is expressed on trophoblastic cells*

**Post-evacuation:**

- Prescribe *contraceptive*
- Follow hCG levels *weekly until normal x3*, then *monthly for 6 months*
TREATMENT

For patients who do not wish to preserve fertility, *hysterectomy* may be performed as an alternative to suction evacuation

- The high cost and risk should limit this procedure to high risk individuals (> 40, hcg > 100,000, ect)
- Patients should still be followed with serial hCG, because ~ 3-5% risk of postmolar GTN
FOLLOW-UP

- **Contraception** is recommended for 6 months after first normal hCG so that any postmolar elevation in hCG can be distinguished
- **OCPs are preferred**, because they suppress LH and remove interference with assay
- They do NOT increase risk of postmolar GTN

**Pregnancy after hydatidiform mole:**

- All women with a history of molar pregnancy have a higher risk of developing malignant disease in subsequent pregnancies
- **Pathologic** evaluation of placenta and measurements of hCG 6 weeks postpartum are recommended
PERSISTENT GTD / POSTMOLAR GTN

- Postmolar invasive mole or CCA occurs in ~ 15-20% of complete and 1-5% of partial molar pregnancies

- Only 2-3% of all molar pregnancies will progress into CCA

- Of women with invasive mole, ~ 15% will have metastatic disease to the lung or vagina

- The likelihood of persistent GTD after molar pregnancy is higher if hCG > 100,000, excessive uterine size (> 20 wks), and theca lutein cysts > 6 cm

  - Women with 1 of these have 40% risk; with none of these features, they have 4%

- For women with persistent GTD, second curettage can be considered if WHO score is < 5
QUIESCENT GTD

- Some women with history of GTD may have consistently low levels of hCG (< 200) for at least 3 months, but no detectable disease.
- There is no evidence of hyperglycosylated hCG.
- This quiescent GTD does not respond to surgery or chemotherapy.
- It is believed that there is individual, slow-growing syncytiotrophoblast cells that have no invasive potential.
- ~25% go on to develop GTN.
- Have to closely monitor these patients with periodic hCG levels and they should avoid pregnancy.
GESTATIONAL TROPHOBLASTIC NEOPLASIA
CLINICAL PRESENTATION

- Postmolar GTN, either invasive mole or CCA, presents with *irregular bleeding* after evacuation of a hydatidiform mole
- *Persistent hCG elevation*
  - Following evacuation of molar pregnancy, think invasive mole vs CCA
  - Following normal pregnancy, miscarriage, or ectopic pregnancy, think CCA vs PSTT
- CCA can develop after any pregnancy, with 25% occurring after abortion of tubal pregnancy; 50% after molar pregnancy (extremely rare following partial molar pregnancy)
- Pulmonary symptoms: dyspnea, cough, chest pain, respiratory failure
- Neurologic symptoms: vomiting, seizures, headaches, hemiparesis, speech or visual disturbances
DIFFERENTIAL DIAGNOSIS

**Depends on the history and clinical presentation:** key issue is to determine the *antecedent pregnancy* was a molar or nonmolar pregnancy, and when it was terminated

- Following **molar pregnancy**, the diagnosis of GTN is generally clearly established with serial measurements of hCG
- Following **nonmolar pregnancy**, the differential is more challenging
  - Pregnancy; multiple gestations
  - SAB
  - Ectopic pregnancy
  - Other neoplasms (germ cell ovarian tumor); ectopically-produced hCG from nontrophoblastic tumors (bladder, stomach, liver, pancreas, myeloma, melanoma)
  - Pituitary hCG or phantom hCG
CHORIOCARCINOMA

- Highly malignant epithelial tumor
- Can arise after any type of pregnancy, but rarely following partial molar pregnancy
- Sheets of anaplastic trophoblastic tissue without chorionic villi
  - IHC stains strong for hCG, inhibin, cytokeratin, and Ki-67
- Most lesions begin in the uterus; most common site of metastases is lung (80%), vagina (30%), brain (10%), liver (10%), spleen, then GI tract
- *This is the most common diagnosis of GTN following a non-molar pregnancy; this should be the presumed diagnosis, unless proven otherwise*
PLACENTAL SITE TROPHOBLASTIC TUMOR

- Potentially malignant tumor that arises from intermediate trophoblastic cells
- Only ~ 300 cases reported; can occur months / years after pregnancy
- Most common is following term pregnancy
- 70% of them act benign; 30% can develop metastasis and cause death
- Monomorphic population of mononuclear trophoblastic cells invading the myometrium
  - IHC for hPL, CD 146
- *Fairly resistant to chemotherapy*
EPITHELIOID TROPHOBLASTIC TUMOR (ETT)

- Rare, only 52 reported cases
- Similar to PSTT
- Most diagnosed following term pregnancy
- Monomorphic trophoblastic cells similar to PSTT, but smaller and contain clear cytoplasm
DIAGNOSIS

FIGO criteria: it is a clinical diagnosis! Tissue is not mandatory

1. hCG plateau lasting for 4 measurements over a period of at least 3 weeks (D1, 7, 14, 21)
2. Rise in hCG of 10% or more for 3 measurements over at least 2 weeks (D1, 7, 14)
3. Persistent hCG 6 months after evacuation
4. Histologic diagnosis of CCA

Established GTN:

- Metastatic work-up and evaluation of risk factors
- CBC, CMP, coags, type and screen, hCG, CXR; TSH if > 100,000
- If CXR abnormal, then obtain CT of CAP; consider brain MRI
STAGING AND RISK SCORING

- WHO risk scoring takes into account 8 criteria, scored 0-4
- Used for selecting initial therapy for patients with GTN
- This staging / scoring does not apply to PSTT or ETT
## Stage Description

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Disease confined to uterus</td>
</tr>
<tr>
<td>II</td>
<td>Disease extends outside uterus but is limited to genital structures (adnexa, vagina, broad ligament)</td>
</tr>
<tr>
<td>III</td>
<td>Disease extends to lungs with or without genital tract involvement</td>
</tr>
<tr>
<td>IV</td>
<td>Disease involves other metastatic sites</td>
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</tbody>
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## Risk Factor Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
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<tbody>
<tr>
<td>Age, years</td>
<td>≤39</td>
<td>&gt;39</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Mole</td>
<td>Abortion</td>
<td>Term</td>
<td></td>
</tr>
<tr>
<td>Pregnancy event to treatment interval, months</td>
<td>&lt;4</td>
<td>4–6</td>
<td>7–12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Pretreatment hCG, mIU/mL</td>
<td>&lt;10^3</td>
<td>10^3–10^4</td>
<td>10^4–10^5</td>
<td>&gt;10^5</td>
</tr>
<tr>
<td>Largest tumor mass, including uterus, cm</td>
<td>&lt;3</td>
<td>3–4</td>
<td>≥5</td>
<td>–</td>
</tr>
<tr>
<td>Site of metastases</td>
<td>–</td>
<td>Spleen, kidney</td>
<td>GI tract</td>
<td>Brain, liver</td>
</tr>
<tr>
<td>No. of metastases</td>
<td>–</td>
<td>1–4</td>
<td>5–8</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Previous failed chemotherapy</td>
<td>–</td>
<td>–</td>
<td>Single drug</td>
<td>≥2 drugs</td>
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MANAGEMENT

- The cure rate for high-risk GTN (usually CCA), is > 90%
- Trophoblasts are inherently sensitive to chemotherapy and we have excellent marker (hCG) to follow
- Management of PSTT and ETT is more challenging, because they do not respond to chemotherapy

Low-risk GTN:

- Stage I, or stage II or III with risk score of < 7
- Stage I, with WHO score 0-4 may benefit from second curettage
- When chemotherapy is indicated, treat with single-agent methotrexate or actinomycin D
- Several different protocols; the 5-day methotrexate or the 8-day MTX-folinic acid protocol is more effective than weekly IM MTX (NO LONGER RECOMMENDED)
- Common side effects: stomatitis, mucositis, GI symptoms, pleurisy, skin rash
MANAGEMENT

- Chemotherapy is continued until hCG have returned to normal, and at least 2 additional cycles is administered after a normal value
- Primary treatment failure occurs in 10-30% of low-risk GTN, and 30-50% of low-risk, metastatic GTN
- Most will still obtain remission after changing regimens

High-risk GTN:

- Stage IV disease, or stage II or III with risk score > 6
- Treated with multiagent chemotherapy (EMA-CO)
  - Etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine
- Cure rates 80-90%; usually treat 3-4 cycles after normalization
MANAGEMENT

PSTT and ETT:

- Measurement of the *free beta subunit* may be helpful since hCG is not terribly elevated

- Because of the high rates of lymphatic spread and relative resistance to chemotherapy, *hysterectomy with lymph node dissection* is the recommended treatment

- Chemotherapy (EMA-EP) is treatment of choice for metastatic disease
FOLLOW-UP

After hCG has returned to normal and treatment has been completed, obtain hCG levels *monthly for 12 months*

- Risk of relapse is ~ 3% *in the first year*; drops to < 1% thereafter
- Most women resume normal ovarian function after chemotherapy and can achieve pregnancy
- Pelvic ultrasound is recommended in 1st trimester of any post-GTN pregnancy to confirm normal pregnancy
- Products of conception should be sent to pathology and obtain hCG at 6 weeks postpartum
RESOURCES

NCCN: Gestational Trophoblastic Neoplasia; Version 2. 2020